Vitamin D and pregnancy

Vitamin D deficiency and associations with gestational diabetes and neonatal body composition in a multi-ethnic population.

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PREFACE, ACKNOWLEDGEMENTS AND FUNDING

Preface

As a general practitioner who has worked with immigrants for several years, I was increasingly aware of vitamin D deficiency re-emerging as a medical issue. Based on health examinations of recently arrived immigrants from Africa and Asia, I found severe vitamin D deficiency among children, adolescents and adults, including pregnant women. At that time, the prevalence of deficiency among most ethnic minorities in Norway was unknown, and available guidelines did not give clear recommendations for treatment of vitamin D deficiency. I was particularly concerned about pregnant women and children with severe deficiency, and in 2009, I contacted paediatricians, endocrinologists, obstetricians and the antenatal care unit at Oslo University Hospital. I received strikingly divergent advice for treatment from a maintenance dose of 10 μg/day of vitamin D_3 to high-dose vitamin D_2 supplementation. This resulted in a deeper concern about the safety issues associated with treating pregnant women with a high dose of vitamin D_2. At a later stage, with this concern in my mind, I had the opportunity to join the STORK Groruddalen study group that already had performed a study from 2008-2010 of pregnant women and their newborns. I was given the opportunity to use already collected data to explore vitamin D status and clinical outcomes among pregnant women and their neonates in a multi-ethnic population.

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NORSK SAMMENDRAG – NORWEGIAN SUMMARY

Det overordnete målet med prosjektet var å øke kunnskapen om vitamin D-status og vitamin D-mangel blant gravide i en multi-etnisk befolkning i Oslo, Norge. Vi brukte data fra en populasjonsbasert kohortstudie av 823 friske, gravide kvinner som fikk svangerskapsomsorgen ved helsestasjoner i Groruddalen, og deres nyfødte barn (STORK Groruddalen-studien). Data fra spørreskjema, målinger og blodprøver av mor ble innsamlet i svangerskapsuke 15 og 28, og kliniske målinger av den nyfødte ved fødsel.

Vi fant at ca. 80% av kvinnene fra Sør-Asia, Midtøsten og Afrika hadde vitamin D-mangel (definert som 25-hydroksyvitamin D [25(OH)D] <50 nmol/L) tidlig i svangerskapet, sammenlignet med 20 % av vest-europeiske kvinner. Andelen som brukte vitamin D-tilskudd i svangerskapet var lavere blant etniske minoritetskvinner fra Asia og Afrika sammenlignet med vest-europeiske kvinner. Kvinner med vitamin D-mangel ble anbefalt vitamin D-tilskudd. Blant disse kvinnene hadde både andelen som tok vitamin D-tilskudd, og vitamin D-nivået, økt signifikant ved oppfølgingsbesøket i uke 28 av svangerskapet. I ujusterte analyser fant vi en signifikant sammenheng med vitamin D-mangel og både svangerskapsdiabetes og barnets fødselsvekt og kroppssammensetning. I justerte regresjonsanalyser fant vi imidlertid ingen uavhengig assosiasjon mellom 25(OH)D i svangerskapet og svangerskapsdiabetes eller andre mål på redusert glukosetoleranse blant kvinnene. Vi fant heller ingen uavhengig assosiasjon mellom maternell 25(OH)D i svangerskapet og fødselsvekt eller andre antropometriske mål av den nyfødte.

Avhandlingen har tilført ny kunnskap om vitamin D status hos gravide, ikke minst i Norden, ved å se på ulike etniske grupper samtidig. Vitamin D mangel var utbredt blant gravide fra Sør-Asia, Midtøsten og Afrika, men dette forklarte ikke den høye forekomsten av svangerskapsdiabetes eller lavere fødselsvekten i noen av de etniske gruppene.

ENGLISH SUMMARY

The overall goal was to increase our knowledge about vitamin D status and vitamin D deficiency in pregnancy in a multi-ethnic population in Oslo, Norway. We used data from the STORK Groruddalen study, a population-based cohort of 823 healthy, pregnant women attending primary antenatal health care units in Groruddalen, and their neonates. Maternal data from questionnaires, measurements and blood samples were collected at 15 and 28 weeks of gestation and clinical measurements of the newborn at birth.

We found that approximately 80% of pregnant women from South Asia, Middle East and Africa had vitamin D deficiency (defined as 25-hydroxyvitamin D [25(OH)D] <50 nmol/L) in early pregnancy, compared with 20% of Western European women. The proportion of women using vitamin D supplementation in pregnancy was lower among ethnic minority women compared with Western European women, but both the proportion using supplements and mean 25(OH)D increased significantly in vitamin D-deficient women who received a simple recommendation for supplementation. In unadjusted analyses, we found an association with maternal vitamin D deficiency and both gestational diabetes and body composition of the newborn. However, after adjustments, we found no independent associations between 25(OH)D during pregnancy and gestational diabetes or other measures of glucose metabolism among the women. Additionally, we found no independent associations between maternal 25(OH)D during pregnancy and birth weight or other anthropometric measures of the newborn.

Ours studies have added new knowledge about vitamin D status among pregnant women in multi-ethnic societies. Pregnant women from South Asia, Middle East and Africa had a high prevalence of vitamin D deficiency, but vitamin D deficiency could not explain the high prevalence of gestational diabetes or the lower birth weight found in some ethnic minority groups.

LIST OF PAPERS

I. Eggemoen AR, Falk RS, Knutsen KV, Lagerlov P, Sletner L, Birkeland KI, Jenum AK. Vitamin D deficiency and supplementation in pregnancy in a multiethnic population-based cohort. BMC Pregnancy and Childbirth. 2016;16(1):7. doi: 10.1186/s12884-016-0796-0.

II. Eggemoen AR, Waage CW, Sletner, L, Gulseth HL, Birkeland KI, Jenum AK. Vitamin D, gestational diabetes and measures of glucose metabolism in a population-based multi-ethnic cohort. (Submitted to Journal of Diabetes Research October 14th 2017)

III. Eggemoen AR, Jenum AK, Mdala I, Knutsen KV, Lagerlov P, Sletner L. Vitamin D levels during pregnancy and associations with birth weight and body composition of the newborn: a longitudinal multiethnic population-based study. British Journal of Nutrition. 2017; May 4:1–9. doi:10.1017/S000711451700068X.

ABBREVIATIONS, DEFINITIONS AND TERMS

Abbreviations

25(OH)D: 25-hydroxyvitamin D, also called calcidiol

AHRQ: Agency for Healthcare Research and Quality

BMI: body mass index

CVD: cardiovascular disease

DBP: vitamin D binding protein

DAG: Directed acyclic graph

DEQAS: Vitamin D External Quality Assessment Scheme

FPG: fasting plasma glucose

GDM: gestational diabetes mellitus

GP: general practitioner

GRADE: Grading of Recommendations Assessment, Development and Evaluation

GW: gestational week

HOMA: homeostatic model assessment

HOMA-IR: homeostatic model assessment of insulin resistance

HOMA-B: homeostatic model assessment of β-cell function

IOM: Institute of Medicine in the US (renamed the National Academy of Medicine)

IU: international units

LC-MS/MS: liquid-chromatography–tandem mass spectrometry

NICE: National Institute for Health and Care Excellence

PG: plasma glucose

RCT: randomized controlled trial

SGA: small for gestational age

SPSS: Statistical Package for the Social Sciences

UK: United Kingdom

US: United States of America

UVB: ultraviolet radiation B

WHO: World Health Organization

Definition of deficiency used in this thesis

Vitamin D deficiency: 25(OH)D <50 nmol/L

Severe vitamin D deficiency: 25(OH)D <25 nmol/L

The Hormone Laboratory's lower reference range of 25(OH)D: <37 nmol/L (Oslo University Hospital)

Conversion of relevant vitamin D units

25(OH)D concentration:

- 1 nmol/L = 2.5 × ng/mL
- 50 nmol/L = 20 ng/mL

Vitamin D intake dose:

- 1 μg = IU/40
- 10 μg = 400 IU

INTRODUCTION

Vitamin D

Vitamin D is important for bone metabolism in the body as it increases the intestinal absorption of calcium, which is essential for skeletal health. Vitamin D is called a vitamin, but is actually a steroid pro-hormone acting in different locations in the body. The vitamin D status of an individual is a result of both the environment and genetics. The major source of vitamin D is synthesis in the skin when exposed to the sun. In addition, vitamin D is absorbed from the diet and from supplements. Only a very few foods contain vitamin D. The habits of sun exposure, types of clothing worn, age and latitude all affect the production of vitamin D in the skin. In addition, supplementation intake, skin pigmentation and different genotypes of vitamin D binding protein and enzymes may affect the vitamin D status.

Worldwide vitamin D status

Vitamin D levels have been reported from all continents and from most countries (1, 2). In Europe, vitamin D status varies, with higher levels in Northern than in Southern regions, and higher in Western than in Eastern countries (1-3). Despite a long winter with little sunshine, vitamin D status is often sufficient in Scandinavia. The inverse North–South gradient found in Europe is probably due to a relatively high fatty fish and cod liver oil intake in the Nordic countries (1, 4, 5). In general, vitamin D status is adequate in North America, although large variations in vitamin D levels are observed between different ethnic groups (1, 2). In the Middle East, vitamin D status differs according to the clothing worn and gender; completely veiled women have the lowest serum levels of vitamin D (1-3, 6). In Asia, vitamin D status is generally low, except in South-East Asia (1-3, 6). In Africa, serum levels of vitamin D are reported to be relatively high, although fewer studies have been done; but also here, lower serum levels were found in veiled women (1, 6). However, data on vitamin D levels from particularly deprived countries or countries with political instability, conflicts or war are lacking. In addition, population-based data are not available for most countries in Africa. Only a few studies from Central and South America exist, and data from

several countries are lacking (1-3). Available studies indicate almost adequate vitamin D status, with a gradient with highest vitamin D levels near the equator. In Oceania, the vitamin D levels are higher, but with a large seasonal variation in serum levels in New Zealand (1, 2).

In general, population-based studies are only available from Europe, North America and Oceania, while studies from the Middle East, Asia, Africa, Central and South America are mostly clinical studies of selected population groups (1, 3). Comparisons of studies are also hampered by different analytical methods for measuring vitamin D status. Large variation in the levels of vitamin D exists across the world, and studies indicate a low or suboptimal vitamin D status in many countries, with the lowest vitamin D status in the Middle East and South Asia (1-3, 6).

Vitamin D deficiency

Definition

According to present standards, the best indicator of an individual's vitamin D status is the serum level of total 25-hydroxyvitamin D [25(OH)D] (7-9). The gold standard method for measuring vitamin D status is to determine the serum concentration 25(OH)D by liquid chromatography–tandem mass spectrometry (LC-MS/MS) (10). However, differences in analytical methods for measurement of 25(OH)D are widespread, and most studies from recent decades have used immunoassay methods to determine the 25(OH)D concentration. Further, the variation among laboratories using different immunoassays may be as high as 30%, and it is therefore important to interpret studies using different immunoassays with caution (1-3). The Vitamin D External Quality Assessment Scheme (DEQAS) was established to ensure the analytical reliability of 25(OH)D, and 1200 laboratories from 54 countries are participating (http://www.deqas.org). Further, a protocol for standardizing 25(OH)D worldwide has been developed by the National Institutes of Health in US; called the Vitamin D Standardization Program (VDSP) (https://ods.od.nih.gov/Research/vdsp.aspx) (11, 12).

Vitamin D deficiency is usually defined as 25(OH)D <50 nmol/L, without relation to clinical symptoms (7, 9, 13). Clinical symptoms of longstanding vitamin D deficiency are related to bone health, with a threshold of 25(OH)D <25 nmol/L (8, 13). However, there is no agreement about the optimal concentration of 25(OH)D for skeletal health (14); suggestions are based on several criteria, including maximal suppression of parathyroid hormone, adequate intestinal absorption of calcium and prevention of fractures (15). The Institute of Medicine (IOM) recommends that the serum concentration of 25(OH)D should be >50 nmol/L, with an optimal concentration of 50–100 nmol/L (9, 14). This is controversial and the Endocrine Society has suggested a lower limit of 75 nmol/L to maximize the effect of vitamin D on calcium, bone and muscle metabolism, with an optimal concentration of 25(OH)D of 75–125 nmol/L (16, 17). Most experts agree that levels <50 nmol/L are suboptimal for skeletal health and that the optimal concentration lies in the range of 75–100 nmol/L (15).

Prevalence of vitamin D deficiency

Using a vitamin D level <50 nmol/L as the definition of deficiency, there is a high prevalence in adults worldwide, especially in the Middle East and South Asia where about 80–90% may be deficient (1, 2, 18). Large ethnic differences in vitamin D levels have been reported in the US and Europe (1, 6, 7, 19-23). African-Americans and Hispanics have higher prevalence of vitamin D deficiency compared with white Americans (1, 7, 20, 23). The prevalence of vitamin D deficiency in European populations is estimated to be about 40% overall (4, 22), but a much higher prevalence of vitamin D deficiency is observed among ethnic minorities living in Europe (4, 6, 24). Non-Western immigrants living in the UK and the Netherlands have a higher prevalence of vitamin D deficiency compared with ethnic Europeans (6, 20).

In Norway too, vitamin D deficiency is more prevalent among immigrants from the Middle East and Asia compared with ethnic Norwegians (25) while the vitamin D status in the majority population is good (26, 27). However, the prevalence of deficiency is higher in certain subgroups such as adolescents, females and the elderly

(26, 28). A high prevalence of deficiency has been found in ethnic groups primarily from Pakistan, Iran, Turkey, Sri Lanka and Vietnam (25, 26, 29-33). Immigrants from Sri Lanka living in Norway had lower vitamin D status than individuals living in their country of origin (29). In Norway, the number of immigrants is increasing, and a study of vitamin D status among recently arrived immigrants with ethnic origin from Asia and Africa found a high prevalence of deficiency, with women and adolescents having the lowest levels (34). Widespread vitamin D deficiency has been found in a study among Somali, Pakistani and Turkish postpartum women and their infants (35) and among immigrants from South Asia, the Middle East and Africa (31, 33).

Risk factors for deficiency

Exposure to ultraviolet radiation B (UVB) from the sun and dietary intake of vitamin D determine an individual's vitamin D status; intake through diet accounts for 10–20% while the sun is the main source (7, 15, 36). Exposure of the skin to UVB radiation (290–315 nm) causes production of pre-vitamin D_3 from 7-dehydrocholesterol (37-39). Low sun exposure reduces cutaneous production of pre-vitamin D_3 and thereby the concentration of 25(OH)D. Factors such as clothing style, use of sunscreen, avoidance of the sun, skin pigmentation, higher latitude and winter season will all affect the production (18). Aging reduces 7-dehydrocholesterol in the skin, leading to a subsequent reduction of the skin's synthesis of pre-vitamin D_3, and thereby reduced production of 25(OH)D (40). At latitudes above 42°N/S of the equator, there will be no cutaneous production during winter (41). During the summer, only sun exposure in the middle of the day implies cutaneous production at these latitudes, as the angle at which the sunlight passes through the atmosphere is critical to UVB radiation being absorbed in the atmosphere (20, 42). Although UVB radiation is the major source of vitamin D status, the dietary intake is especially important during periods with low sun exposure (43). The dietary sources are mainly fatty fish, cod liver oil, vitamin D supplements and fortified food (cheese, butter, milk) (7). Vitamin D is fat-soluble and stored in fat tissue, and an inverse association between serum levels of 25(OH)D and BMI exists (44, 45).

Therefore, known risk factors for vitamin D deficiency are low sun exposure, physiological factors such as skin pigmentation, older age, obesity and malabsorption, and low dietary intake of fatty fish or supplements (3, 18, 20).

Groups at risk of vitamin D deficiency are adolescents, young children, females, the elderly especially if institutionalized, pregnant women and their newborns, and those of ethnic origin from the Middle East or South Asia (1, 26). Ethnic minorities with other cultural practices migrating to higher latitudes are at risk; darker skin pigmentation, avoidance of exposure to the sun and low dietary intake of both fish and supplements increase the risk (2, 6, 46). In particular, women wearing a veil and full-length clothing may have undetectable levels of 25(OH)D (1). In addition, a positive association with socio-economic status and adequate vitamin D status has been found in several populations (2, 3).

Associations of vitamin D status with health outcomes

Vitamin D deficiency has been associated with a range of health outcomes including all-cause mortality (18, 47-51).

Bone health

Adequate vitamin D status is important for bone health (9, 37, 50, 52). In children, vitamin D deficiency causes rickets, with potentially long-lasting effects (37, 53, 54). In adults, vitamin D deficiency may cause osteoporosis and osteomalacia (8, 15). Maternal vitamin D status has been associated with reduced bone mineral content in children at the age of nine years (55), but in a randomized controlled trial (RCT) no difference in neonatal whole-body bone mineral content was observed between neonates born to mothers receiving placebo or vitamin D supplementation (1000 IU/d) (56). Sufficient vitamin D status seems to protect against musculoskeletal diseases such as fractures and muscle weakness in RCTs among elderly (15), although results are inconsistent (15, 57).

Despite there being widespread vitamin D deficiency in ethnic minority groups, this does not seem to translate into clinical diseases such as osteoporosis at the same level of 25(OH)D as in the majority population (46, 58, 59). People of Pakistani origin

living in Oslo have a much higher prevalence of vitamin D deficiency and secondary hyperparathyroidism, but seem to have similar bone mineral density compared with ethnic Norwegians (30). The widespread vitamin D deficiency in ethnic minority groups, with less-than-expected evidence of negative health outcomes, is a paradox.

Non-skeletal outcomes/health effects

Vitamin D deficiency has been associated with a wide range of non-skeletal diseases such as cardiovascular disease (CVD), cancer, diabetes, infectious disease and autoimmune diseases in observational studies (18, 47-49). However, conclusive evidence about a causal relationship is still lacking for most outcomes other than bone health. During recent years, several RCTs of vitamin D supplementation found no clear effect for health outcomes such as CVD, cancer, diabetes, muscle strength, pain, infectious disease, or autoimmune diseases (33, 48, 57, 60-62). However, a recent systematic review and meta-analyses found that vitamin D supplementation reduced the risk of acute respiratory tract infections (63). Another systematic review and meta-analyses concluded that most RCTs have been performed in populations without low vitamin D levels and therefore absent of an effect does not disprove adverse health outcomes for low vitamin D levels (51).

High levels of vitamin D have been associated with negative health outcomes such as CVD stroke and acute myocardial mortality (64), prostate cancer (65) and increasing falls and fractures in older adults (66), and IOM suggests awareness of concentrations >125 nmol/L (8).

Exploring causal relationships is highly important for the observed associations of low vitamin D status with negative health outcomes. Very large ongoing RCTs (VITAL (NCT01169259), FIND (NCT01463813), D-Health (NCT01537809) and VIDAL (ISRCTN46328341)) will probably answer the questions about causal relations for cancer, CVD and total mortality (67).

Vitamin D and pregnancy

Metabolism of vitamin D during pregnancy

The 25(OH)D passes the placenta barrier and is converted to the active form on the foetal side of the placenta and in the foetal kidneys. The foetal cord blood concentration correlates strongly with the maternal concentration (18, 68, 69). The maternal concentration of total serum 25(OH)D during pregnancy is relatively constant, although a slight decrease during the last trimester of both the total and the free fraction of 25(OH)D has been observed (70-72). Despite haemodilution in pregnancy, the levels of vitamin D binding protein (DBP) increases, probably conserving maternal 25(OH)D from the maternal renal filtration system (18, 70).

Prevalence of vitamin D deficiency

Vitamin D deficiency in pregnancy is prevalent worldwide, as reported in non-gestational women, and women with limited sun exposure due to clothing style or outdoor activity, and low dietary intake of vitamin D are at risk (73-76). Especially among women living in the Middle East and Asia, the prevalence is high, also in pregnancy (6, 75).

In Europe, vitamin D deficiency among pregnant women is observed in the majority populations, although severe vitamin D deficiency is almost non-existent (44, 72, 77, 78). In contrast, severe vitamin D deficiency is prevalent in pregnant minority women living in the Netherlands (79) and UK (77, 80). Little is known of vitamin D status among women with ethnic origin from the Middle East, Asia and Africa living in Northern Europe, although high prevalence has been reported in small studies among Somali, Pakistani and Bangladeshi women living in Norway, Sweden and Finland (25, 81-85). However, there is a lack of population-based studies exploring vitamin D status in pregnancy in the multi-ethnic Europe of today.

Adverse pregnancy and neonatal outcomes

Vitamin D deficiency in pregnancy is associated with adverse maternal and child health outcomes in observational studies (86-89), and RCTs have suggested possible protective effects of supplementation (90, 91). Some have raised concerns about the

foetus developing in an environment of low 25(OH)D concentrations (91, 92). Maternal vitamin D deficiency has been associated with low birth weight, small for gestational age newborns, preterm delivery, as well as with reduced bone mass and low postnatal calcium concentrations, although studies show inconsistent relationships (57, 87, 90, 91, 93). In addition, gestational diabetes mellitus (GDM) and pre-eclampsia have been associated with deficiency during pregnancy (8, 86, 94, 95). Trials examining the safety and efficacy of vitamin D supplementation in pregnancy have concluded that vitamin D supplementation is safe and significantly improves 25(OH)D levels (96-101). A Cochrane review of RCTs from 2016 found indications that vitamin D supplementation might increase neonatal length and head circumference, reduce the risk of pre-eclampsia, low birth weight and preterm birth, but when combined with calcium supplementation, the risk of preterm birth increased (75). The Cochrane review found no effect on GDM, caesarean section, stillbirths or neonatal deaths, but the studies were few and in general of low quality. The conclusion was that it was still unclear whether vitamin D supplementation should be routinely recommended in pregnancy (75).

Gestational diabetes, prevalence and risk factors

GDM has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy (102, 103). Women with GDM have a 7-fold increased risk of developing type 2 diabetes compared with normoglycaemic pregnancy (104, 105). They also have increased risk of CVD (105, 106). The diagnostic criteria for GDM were primarily set to identify women predisposed to develop type 2 diabetes later in life, who also had increased risk of pregnancy complications (WHO_{1999} criteria) (102). In 2013, WHO proposed new criteria (WHO_{2013} criteria) based on adverse effects on the offspring (107). Globally, the prevalence of GDM is increasing, not least due to demographic and epidemiological transitions, with increasing maternal age for their first pregnancy in many countries, and societal changes in diet and less physical activity (106). These changes lead to an increase in the prevalence of overweight, obesity and sedentary behaviour in women of reproductive age, all risk factors for GDM (106). In Europe, immigration of groups with risk for type 2 diabetes, also contributes to the increasing prevalence. In addition, family history of diabetes,

GDM in previous pregnancies and previous delivery of a macrosomia newborn are other risk factors for GDM (95, 108).

GDM increases the risk of macrosomia and related complications like caesarean section, operative vaginal delivery, shoulder dystocia, and neonatal hypoglycaemia and hyperbilirubinemia (104, 109). GDM also increases the risk of maternal hypertension and preeclampsia (109, 110). Systematic reviews and meta-analyses have stated that treatment reduces clinically important outcomes (110). Different life style interventions for treating GDM have found a reduction of gestational weight gain and improved pregnancy outcomes for both mother and child, with dietary interventions considered more effective and feasible than physical activity interventions among pregnant women at risk of GDM (111). A systematic review and meta-analyses of intervention studies concluded that physical activity in pregnancy have a protective effect against developing GDM (112).

The oral glucose tolerance test is the gold standard diagnostic test for GDM, usually offered in gestational week 24-28 (109, 113). However, there is still no international consensus about diagnostic criteria or screening strategies to identify women with hyperglycaemia in pregnancy. Both insulin resistance and β-cell dysfunction contributes to the development of GDM. Insulin resistance increases about 50-60% during a normal pregnancy, irrespective of the pre-pregnant level, but is exaggerated by excessive gestational weight gain (106, 114). In all pregnant women, pancreatic β-cells must compensate for the pregnancy-induced insulin resistance and secret more insulin in all pregnant women, and in women with insufficient ability to increase their insulin secretion this implicate an increased risk of hyperglycaemia (103, 106). From early pregnancy, overweight and obese women are more insulin resistant compared with normal weight women, and become highly insulin resistant in the second half of their pregnancy (103, 106). This is also the case for pregnant women from South Asia and East Asia, as they are more insulin resistant compared with Western Europeans for the same level of BMI (114). Additionally, South Asian women also seem to be less able to increase their β-cell function mutual to the pregnancy-induced insulin resistance compared with Western Europeans (114). Importantly, GDM reflects both

insulin resistance and reduced β-cell function, and both these components have been found to be associated with vitamin D levels (108).

Associations between vitamin D and gestational diabetes and other measures of glucose metabolism

An association between low levels of 25(OH)D and impaired glucose metabolism and type 2 diabetes mellitus have been found in observational studies, although results from trials have not confirmed a causal relationship (45, 115-117). Also an inverse association between maternal 25(OH)D and GDM has been reported, and systematic reviews and meta-analyses have assessed the relation between 25(OH)D status and GDM in observational studies, although results are inconsistent (87-89, 94, 95, 118-120). Interestingly, subgroup analyses indicates differences based on countries, analytical methods for 25(OH)D measurements, season when 25(OH)D measurements were performed, definition of GDM, maternal age, sample size, adjustment for confounders and study quality (95, 118). The complexity of interactions among individual, lifestyle and geographical factors all affect the results of meta-analyses, and the clinical impact of these studies is limited by the observational design (95). So far, no conclusions have been drawn from systematic reviews and meta-analyses about the effect of vitamin D supplementation could reduce the incidence of GDM or improve glucose metabolism in pregnancy (75, 95, 121, 122). Two reviews of trials concluded that vitamin D supplementation did not influence the incidence of GDM, but few RCTs were found, and larger and better-designed RCTs are necessary to reach a definitive conclusion (75, 122).

Possible biological mechanisms of the association between vitamin D and GDM are through effects on insulin-sensitive tissues, calcium pool dysregulation in the pancreas, genetic variations, inflammation and other risk factors (in particular obesity) (95, 108). In addition, the β-cell function may be directly affected by vitamin D, as both vitamin D receptor and the 1α-hydroxylase enzyme have been found expressed in pancreatic islet, enabling conversion of vitamin D into its active form directly by the β-cell (51, 123). In animal experimental studies, vitamin D deficiency causes impaired pancreatic secretion of insulin (51, 115).

Associations between vitamin D and neonatal anthropometric measures and body composition

Vitamin D is essential for foetal skeletal development (8, 28, 55). A positive association between maternal 25(OH)D and birth weight, length and head circumference have been reported (91), although results are inconsistent (57, 75, 89, 90, 122). Few studies of other anthropometric measures of the neonate have been conducted, and only one has explored the association between maternal 25(OH)D status and abdominal circumference, while only a very few studies have explored associations with skin folds and mid-upper-arm circumferences (91, 124). Two studies have found an association between 25(OH)D and any of the birth outcomes (125, 126) while two found no associations (124, 127). One study measuring body composition using dual energy x-ray absorptiometry (DXA) reported that low maternal 25(OH)D level was associated with low fat mass of offspring at birth, but with greater fat mass at the ages of 4 and 6 years (128).

Globally there are large differences in birth weight, with lower birth weight in low- and middle-income countries compared with high-income countries (129-131). Mean birth weight is several hundred grams lower in countries in South Asia and in low-income South Saharan countries compared with that in Norway (131, 132). Indian neonates had lower birth weight, smaller abdominal circumference, less muscle mass, but similar skin folds compared with babies born in the UK (133). Further, Indian neonates had a higher proportion of visceral, deep and superficial subcutaneous fat in the abdominal region, but less non-abdominal superficial subcutaneous fat (134). This body composition has been called “the thin-fat phenotype”; it seems to track throughout life and is associated with a higher risk of CVD and type 2 diabetes (135). The variation in neonatal body composition due to ethnicity is not well documented in multi-ethnic populations, although smaller abdominal circumference among neonates born to women from low-income countries living in Norway has recently been found in the STORK Groruddalen study (136).

Body composition describes the proportion of lean and fat mass in the body. Lean mass is the sum of muscle mass, bone and internal organs. Fat mass can be categorized

into visceral (intra-abdominal) and subcutaneous fat, with the latter being further categorized into superficial and deep subcutaneous fat. Different techniques are available for measurements of body composition; a four-component model is the gold standard, while two-component models (i.e. dual energy x-ray absorptiometry) is easier to use in infants (137). However, more feasible in large studies are different anthropometric measurements, used to describe "fatness" or to assess subcutaneous fat depots directly, or to calculate body proportions as body mass index (BMI). Measures of birth weight, length, circumferences and skin fold thickness are used; these measures are safe, quick and easy to obtain in clinical settings including neonatal examinations, although standardization of measurements is crucial (137). BMI (kg/m^2) has also been used, although ponderal index (kg/m^3) is considered a better predictor of the body composition in infants.

Summary of associations between low vitamin D levels and GDM and neonatal body composition

To summarize, the rationale for our studies of associations between vitamin D and health outcomes related to pregnancy, is related to public health issues; the increasing prevalence of GDM, with potentially long term complications for both mother and offspring. Furthermore, women with ethnic minority origin have a higher prevalence of both GDM and vitamin D deficiency compared with European women. In addition, neonates with origins from Asia and Africa have lower birth weight compared with neonates of European origin. This has led to concerns that a low concentration of maternal vitamin D during pregnancy may increase the risk of GDM with adverse effect on maternal and neonatal outcomes, including effect on foetal growth. If so, this would necessitate a stronger approach to identifying and treating deficient mothers. A robust association would also lend support to set up a trial to test if vitamin D supplementation could prevent GDM in Norway where vitamin D deficiency in pregnancy is prevalent in some population groups.

Vitamin D guidelines

At present, the recommendations for prevention of vitamin D deficiency and its treatment differ between countries and organizations (Table 1), although almost all

guidelines recommend supplementation to older persons and groups at high risk. Methods for rating the strength of the evidence and the strength of the recommendations differ between the guidelines. I have chosen guidelines from European countries at high latitudes (Nordic Nutrition Recommendation, NICE from the UK and the German Nutrition Society) and WHO, and additionally two guidelines from the US and Canada (Institute of Medicine and Endocrine Society) for comparison (8, 13, 17, 36, 138, 139). Two guidelines used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, while two used the modified framework from the Agency for Healthcare Research and Quality (AHRQ). Both GRADE (140) and AHRQ (141) build on systematic reviews and quality assessments of individual studies, including an overall assessment of the body of evidence for certain outcomes. One possible reason for the striking differences in recommendations despite using similar frameworks might be different target populations; while most of the recommendations are for the general population, the target populations of the Endocrine Society Guideline are populations at risk for deficiency.

Guidelines in pregnancy

There is no consensus of the optimal concentration of 25(OH)D in pregnancy, the optimal dose of vitamin D supplementation or how to treat established vitamin D deficiency. WHO recommends a low dose of 5 μg/d (200 IU) vitamin D to treat vitamin D deficiency and no routine supplementation (142). In contrast, the Nordic countries (13) and the UK guidelines (143) recommend that all pregnant women should take routine supplementation 10 μg/d (400 IU) to prevent vitamin D deficiency – independent of their vitamin D status (Table 1).

Table 1. Recommendations for supplements to prevent and to treat vitamin D deficiency.

Guidelines	*Prevention of vitamin D deficiency*			*Treatment of vitamin D deficiency*			
	Pregnancy Lactating	1–65 years	Elderly	Pregnancy Lactating	1–18 years	1–65 years	Framework
NNR 2012	400 IU/d	400 IU/d [1]	800 IU/d				AHRQ
NICE	400 IU/d	Risk groups [2]	400 IU/d				AgreeII
IOM (DRI 2011)	600 IU/d	600 IU/d	800 IU/d				AHRQ
German Nutrition Society 2012	800 IU/d	800 IU/d [4]	800 IU/d				#
Endocrine Society 2012	1500–2000 IU/d	1500–2000 IU/d [3]	1500–2000 IU/d		2000 IU/d for 6 weeks [5]	6000 IU/d for 8 weeks	GRADE
WHO 2012	No	*	*	200 IU/d			GRADE

[1]>2 year: 400 IU/d, [2]<5 year, teenagers, institutionalized, dark skin: 400 IU/d, [3]1–18 year: 600–1000 IU/d, [4]<1 year: 400 IU/d, [5] inclcuding infants <1year

NNR 2012 (Nordic Nutrition Recommendation)

NICE guidelines (UK): public health guideline (PH56) and clinical guideline Antenatal care (CG62)

IOM: Institute of Medicine (US and Canada) DRI; Dietary Reference Intake

Endocrine Society 2012 (US)

AHRQ (Agency for Healthcare Research and Quality Evidence-based Practice Center; EPC)

Agree II: Method for development of NICE public health guideline

The methodological approach for evidence judgement has been described in detail in German in the guidelines of the German Nutrititon Society (www.dge.de/leitlinie).

GRADE (Grading of Recommendations Assessment, Development and Evaluation system)

** WHO and Food and Agrigulture Organization of the United Nations (FAO) 2004: Expert consultation on Human Vitamn and Mineral Requirements: 0–50 years: 200 IU/d, 51–65 year: 400IU/d, >65 year: 600 IU/D. If skin synthesis is reduced by age, clothing/sunscreen use or during winter at latitudes higher than 42 degrees vitamin D supplementation is recommended.*

Ethnicity and health

Ethnicity

The word "ethnicity" derives from the Greek word *"ethnos",* meaning *"nation, people or tribe".* We use the term "ethnicity" to refer to "the social group to which people belong, and/or are perceived to belong, as a result of certain shared characteristics, including geographical and ancestral origins, with particular emphasis on cultural traditions and languages" (144). Cultural traditions related to dietary habits, religion, language and lifestyle are included in the term ethnicity, and from the literature, we know that 25(OH)D is strongly affected by dietary habits, clothing and sun exposure (3, 20, 28, 44). In addition, it seems that genetics may play a role in the metabolism of vitamin D (18, 145, 146). The term ethnicity partly overlaps with the term "race" regarding inherited biological characteristics, but also includes cultural traditions important for identity. However, after the Second World War, the term ethnicity has essentially replaced the term race in Europe, although the latter is still in use in the US (147).

Both ethnicity and race are related to country of birth, or country of birth of parents or grandparents (ancestral origin), which may be important for self-reported ethnicity. However, even within a country there may be different ethnic groups; e.g. in India and Ethiopia. The term ethnicity is complex and should be used with caution. In multicultural societies, ethnicity is not the same as nationality, which is the nation you belong to by citizenship. In Norway, Statistics Norway registers people's country of origin, including being Norwegian-born to immigrant parents, and their geographic origin. An immigrant is defined as a person who was born abroad to two foreign-born parents who have immigrated to Norway. A person who was born in Norway to two foreign-born parents, and in addition has four grandparents born abroad, is defined as Norwegian-born to immigrant parents (148). In health research, country of birth or country of birth of parents is often used as a proxy for ethnicity (147).

Migration and vitamin D

From previous waves of migration, many countries have a proportion of inhabitants with different ethnicity than the majority population, often called a minority, which may be more vulnerable to vitamin D deficiency. With easy travel, migration has increased dramatically. Humans migrate to find better living conditions, or to escape from war and political conflicts or to find work or education. With an increasing number of conflicts, more humans migrate (149). In our century, within-country migration or emigration to neighbouring countries is common. However, an increasing number migrate over a longer distance to other geographic regions or even to other continents with quite a different culture (150).

Geographic regions and health

According to the WHO, mortality rates and life expectancy differ widely between regions of the world (151). The disease burden related to CVD including stroke, cancer, chronic obstructive pulmonary disease and diabetes is increasing, and there is a shift from communicable diseases (in children) towards non-communicable diseases in adults (152-154). HIV infection and death from AIDS is the leading cause of deaths in women of reproductive age, with complications in pregnancy and childbirth being ranked as number two, with 99% of the latter occurring in low-income countries (155). In addition, complications related to adolescent pregnancies are important causes of death among 15–19-year-old female adolescents.

Life expectancy is lower in low-income countries than in high-income countries, although the mortality among children younger than 5 years has decreased in recent years (151, 156). Communicable diseases such as diarrhoea, pneumonia and malaria are still common among children, especially in South Saharan Africa (152). An unanswered question is whether vitamin D deficiency contributes to non-communicable diseases, adverse pregnancy and neonatal outcomes.

Ethnicity and health

Mortality and morbidity differ among populations. Among immigrants originating from low-income countries who move to high-income countries, the mortality and morbidity are often lower than for the majority population in their new country due to

"the healthy migrant effect" (157, 158). However, this positive difference often diminishes across generations. Among ethnic minority groups, the prevalence of CVD including stroke, type 2 diabetes, perinatal and infant mortality, infectious diseases such as tuberculosis and malaria, some cancers (i.e. liver), hemoglobinopathies, vitamin D deficiency and rickets are higher than in the majority population (147). On the other hand, many cancers including lung, colorectal and breast cancer are less common compared with the majority population (147). The prevalence of hypertension, unhealthy diet, physical inactivity, smoking, dyslipidaemia, overweight and obesity – all risk factors for CVD and diabetes – is higher for some ethnic groups compared with the majority population. In Europe, type 2 diabetes is diagnosed 10–15 years earlier and the mortality from CVD is higher in ethnic minorities from Asia and the Middle East, compared with the majority population (159-161). Type 2 diabetes is much more prevalent among Turks, Moroccans, Lebanese and South Asians living in Western Europe compared with the general population (162-164). In Norway, ethnic minorities from low-income countries also have higher rates of both type 2 diabetes and CVD and a younger age at diagnosis (160, 165, 166).

Ethnic minorities may also have a higher perinatal mortality and more pregnancy-related complications (167). Higher perinatal mortality, stillbirths and increased prevalence of caesarean section have been found among some immigrant groups in Norway (168-170). Low maternal 25(OH)D level has been associated with preterm birth and caesarean section, pre-eclampsia and GDM, but whether these associations are causal for reproductive health outcomes is still unclear (8, 87, 90, 91, 94, 171) .

The health inequalities may at least partly be due to factors from early life that may increase the susceptibility to several chronic diseases. Subtle variations in environmental exposures *in utero* can probably influence a range of neonatal phenotypes, which may affect the risk of adult chronic disease (172). Both type 2 diabetes and CVD are associated with low birth weight (173-175). A rapid change in environment and life-style factors between generations – such that occur when moving from rural to urban areas, or from low-income to high-income countries – may result in an inappropriate environment for the child, often called "the developmental

mismatch" (172). Low birth weight is prevalent in populations with a high prevalence of vitamin D deficiency, and an association between maternal vitamin D deficiency and birth weight and being small for gestational age has been observed (87, 90, 91). Whether vitamin D status during pregnancy is essential for *in utero* development of organs is still unknown (18).

Health literacy

Health literacy is important for making use of available health information, and may influence immigrants' vitamin D status. Health literacy has been defined as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions" (176). A wider preferred definition is public health literacy, and implies more than being able to read basic information (177). The WHO has defined health literacy as "a constellation of skills that are necessary to gain access to, understand and use information to promote and maintain good health" (178).

Health literacy and health outcomes

Studies have found that a high proportion of the adult population have an inadequate (insufficient or problematic) health literacy, which varies between countries (176, 179). Low social status, low education, financial deprivation, younger and older age, are associated with limited health literacy (179). Ethnic minorities often have poor communication skills in the majority language, and less knowledge of the body as well as the nature and causes of disease, due to lower education levels. This may imply lower health literacy than the general population, and may contribute in part to ethnic health disparities (180). Individuals with low health literacy will not be able to act on health care information, which implies a reduced possibility of improving their own health (181).

Limited health literacy represents an important challenge for the health care system and professionals, and should be taken into account when developing health care and public health strategies to improve health and reduce health disparity. While few studies have explored vitamin D and health literacy, one study found a reduced

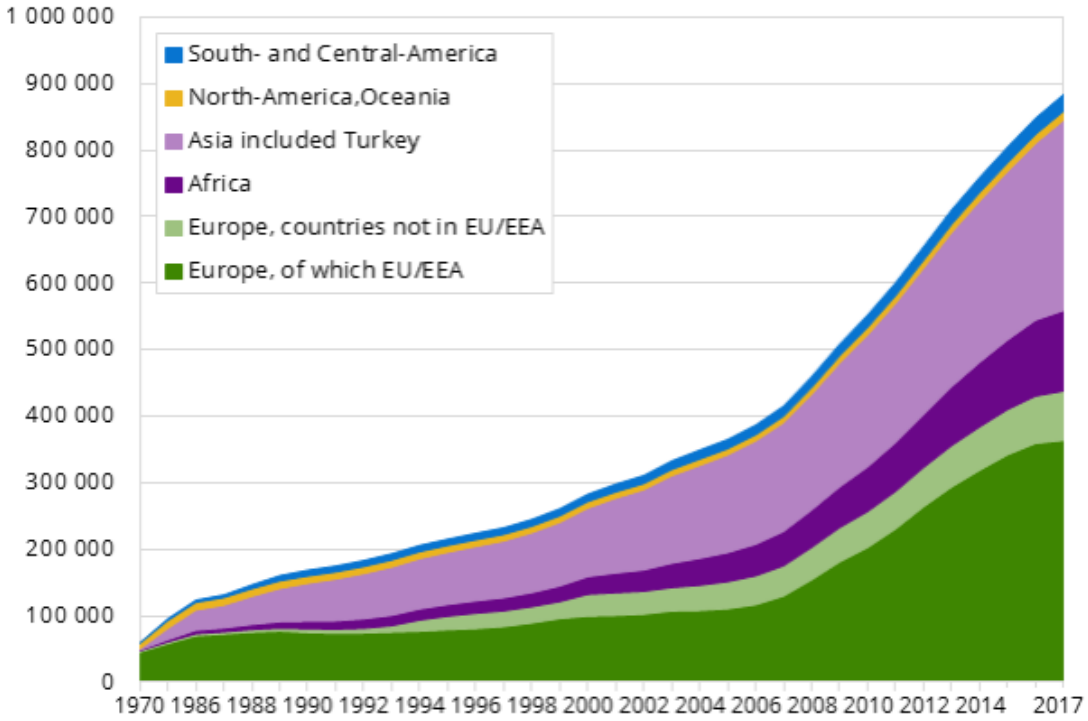
knowledge of vitamin D and dietary sources of vitamin D (77) and one study found that education was associated with the use of supplementation (182).

The Norwegian context

Immigration to Norway has increased over recent years (

Figure 1) (183).

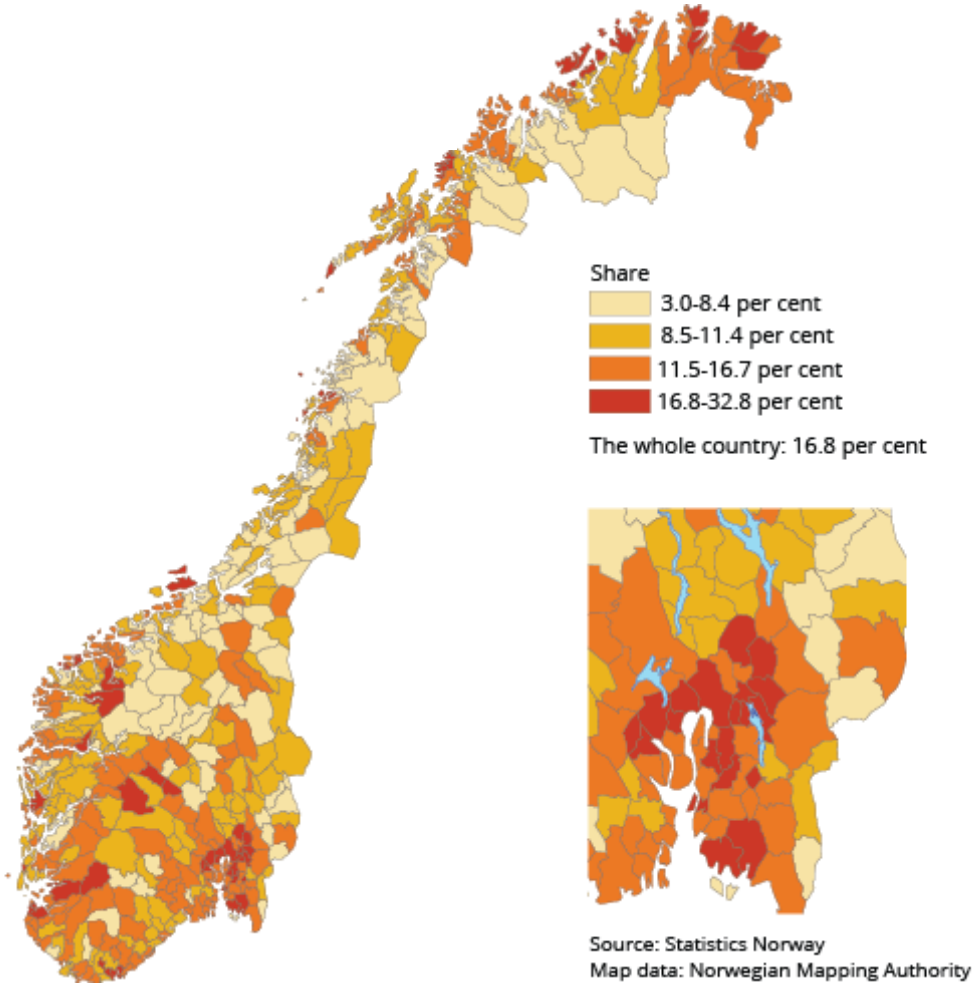
Figure 1. Immigrants and Norwegian-born to immigrant parents, by country background.



Source: Statistics Norway.

The population in Norwegian has become multi-ethnic, especially in the larger cities (Figure 2) (184). Immigrants accounted for 13.8% of the total population in Norway at 1 January 2017 and those who are Norwegian-born to immigrant parents accounted for 3.0% (148). Polish immigrants comprise the largest group, and most who are Norwegian-born to immigrant parents have their background from Pakistan, Somalia and Poland. The proportion of immigrants varies widely across the country, but people with an immigrant background are resident in all municipalities. Oslo has the largest proportion of immigrants in Norway (33% as at 1 January 2017).

Figure 2. Immigrants and Norwegian-born to immigrant parents, as a percentage of the total population in each municipality, as at 1 January 2017.



Norway has a list-based system, with the GPs being responsible for offering appointments and primary health care services. Health services are of relatively low cost for the inhabitants, as the authorities will cover out-of-pocket payments exceeding a pre-specified sum. In addition, pre- and antenatal care are free of charge and easily available from the GPs and at maternal child health clinics.

AIMS OF THE THESIS

The overall goal of this thesis was to increase our knowledge about vitamin D status and vitamin D deficiency among pregnant women in a multi-ethnic society in Oslo, Norway.

The specific objectives were to:

- investigate ethnic differences in vitamin D levels during pregnancy, assess risk factors for vitamin D deficiency and explore the effect of vitamin D supplementation in women identified with low values during early pregnancy (Paper I)
- explore associations between maternal vitamin D level and gestational diabetes and other measures of glucose metabolism (Paper II)
- explore associations between maternal vitamin D level and neonatal birth weight and body composition (Paper III).

We hypothesized a high prevalence of deficiency among ethnic minority pregnant women. We also hypothesized an association between vitamin D levels and gestational diabetes as both the prevalence of vitamin D deficiency and gestational diabetes was high among ethnic minority women. In addition, we hypothesized an association between maternal vitamin D levels in pregnancy and offspring birth weight or one or more components of body composition, because the prevalence of severe deficiency was high and birth weight was low among pregnant ethnic minority women compared with ethnic Europeans.

MATERIALS AND METHODS

The thesis is based on one study of pregnant women. An overview of the study characteristics is given in Table 2 and Table 3.

Tables about Papers I–III:

Table 2. Overview of study characteristics.

Characteristics	***Paper I***	***Paper II***	***Paper III***
Design	Cohort Population-based Prospective		
Primary outcomes	25(OH)D levels (two time points)	Gestational diabetes	Birth weight
Secondary outcomes	Change in 25(OH)D	Other measures of glucose metabolism	Neonatal anthropometric measures
Other variables	See Table 3		
Recommendation of supplementation if 25(OH)D <37 nmol/L	Vitamin D supplements (20 or 30 μg/day) Calcium (1g/day)		
Setting	• Primary Antenatal Health Care, Groruddalen, Oslo Municipality	• Primary Antenatal Health Care, as for Paper I.	• Primary Antenatal Health Care, as for Paper I. • Oslo and Akershus University Hospitals
Participants	• Healthy pregnant women	• Healthy pregnant women	• Healthy pregnant women • their neonates
Ethnic groups	• Western Europe (mostly Norwegians) • South Asia • Middle East/ North Africa • South Sahara Africa • East Asia • Others	• Europe (mostly Norwegians) • South Asia • Middle East/ North Africa • South Sahara Africa • East Asia	• Europe (mostly Norwegians) • Asia • Middle East/ North Africa (incl. Horn of Africa)
Gender	• Women	• Women	• Women • Neonates of both genders

Age range	• 19–45 years	• 19–45 years	• 19–45 years • Newborns (0–72 hours)
Sample size	748	745	719
Year	2008-2011		
Season	Whole year		
Questionnaire	Yes		
Blood samples and analyses	Fasting, analysed consecutively		
Biobank	Yes		
Ethics Committee Registration number	REK 2007/894 REK 2015/1035C		

Table 3. Overview of the characteristics of study variables and outcomes.

Characteristics	***Paper I***	***Paper II***	***Paper III***
Primary outcome variable	Maternal 25(OH)D levels in 15 & 28 GW[1]	Gestational diabetes (28 GW)	Birth weight
Secondary outcome variables	Change in 25(OH)D	• Fasting plasma glucose • 2-hour plasma glucose • Fasting insulin • Fasting C-peptide • HOMA-IR[2] • HOMA-B[3]	• Crown–heel length • Head circumference • Abdominal circumference • Sum of skin folds • Mid-upper-arm circumference • Ponderal index • SGA[4]
Vitamin D supplements	Yes	NA[5]	NA
Gestational week	Yes	NA	Yes
Maternal sum of skin folds	NA	Yes	NA
Change in sum of maternal skinfolds from GW 15 to 28	NA	Yes	NA
Weight gain between pre-pregnancy weight and 28 GW	NA	Yes	NA
Serum-25(OH)D	Yes		
Parity	Yes		
Education	Yes		
Pre-pregnancy BMI	Yes		

[1]GW: Gestational week; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HOMA-B: Homeostatic Model Assessment of β-cell function; [4]SGA: Small for gestational age (preterm was not excluded); [5]NA = not applicable

Vitamin D status measured as 25(OH)D was the primary outcome in Paper I, and the main type of exposure in Paper II and III. We defined vitamin D deficiency as 25(OH)D <50 nmol/L and severe vitamin D deficiency as 25(OH)D <25 nmol/L, in accordance with relevant literature (see page 12(7)).

The terms "ethnicity", "ethnic origin" and "country of birth" are used interchangeably in the papers included in this thesis, all referring to the country of birth of the participant. The terms "geographic origin", "geographic region" and "ethnic group" are also interchangeable, all referring to geographic origin. Ethnicity was defined as the country of birth of the participant. If the participant's mother was born outside Europe or North America, ethnic origin was defined by the participant's mother's country of birth (144, 185).

Papers I-III

Design and setting

The STORK Groruddalen study is a population-based, prospective cohort of healthy pregnant women attending maternal child health clinics for antenatal care in Groruddalen, a multi-ethnic area of Oslo, and their offspring (136, 185). The inclusion period was between May 2008 and March 2010. Groruddalen was selected because the area covers affluent as well as relatively economically deprived residential areas, a population with diverse socio-economic status, and it has a high proportion of women with an ethnic minority background. Further, most pregnant women (75–85%) here attend the maternal child health clinics for antenatal care. To facilitate inclusion of ethnic minority women, information about the study and questionnaires was translated into Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu and Vietnamese and quality checked by bilingual health professionals.

Criteria for inclusion

Eligible participants were pregnant women attending maternal child health clinics or antenatal care in the study period. Inclusion criteria were: 1) lived in the district; 2) planned to give birth at one of the two study hospitals; 3) were <20 weeks' gestation;

4) were not suffering from diseases necessitating intensive hospital follow-up during pregnancy; 5) could communicate in Norwegian or any of the specified languages; and 6) were able to provide written consent to participate.

Source population

The population in the three districts was approximately 82,500 inhabitants at the initiation of the study. The source population consisted of 1918 pregnant women attending the maternal child health clinics for antenatal care during the inclusion period, and 1114 women were eligible for inclusion; see Figure 3 and Appendix (Flow chart for the STORK Groruddalen study (185)).

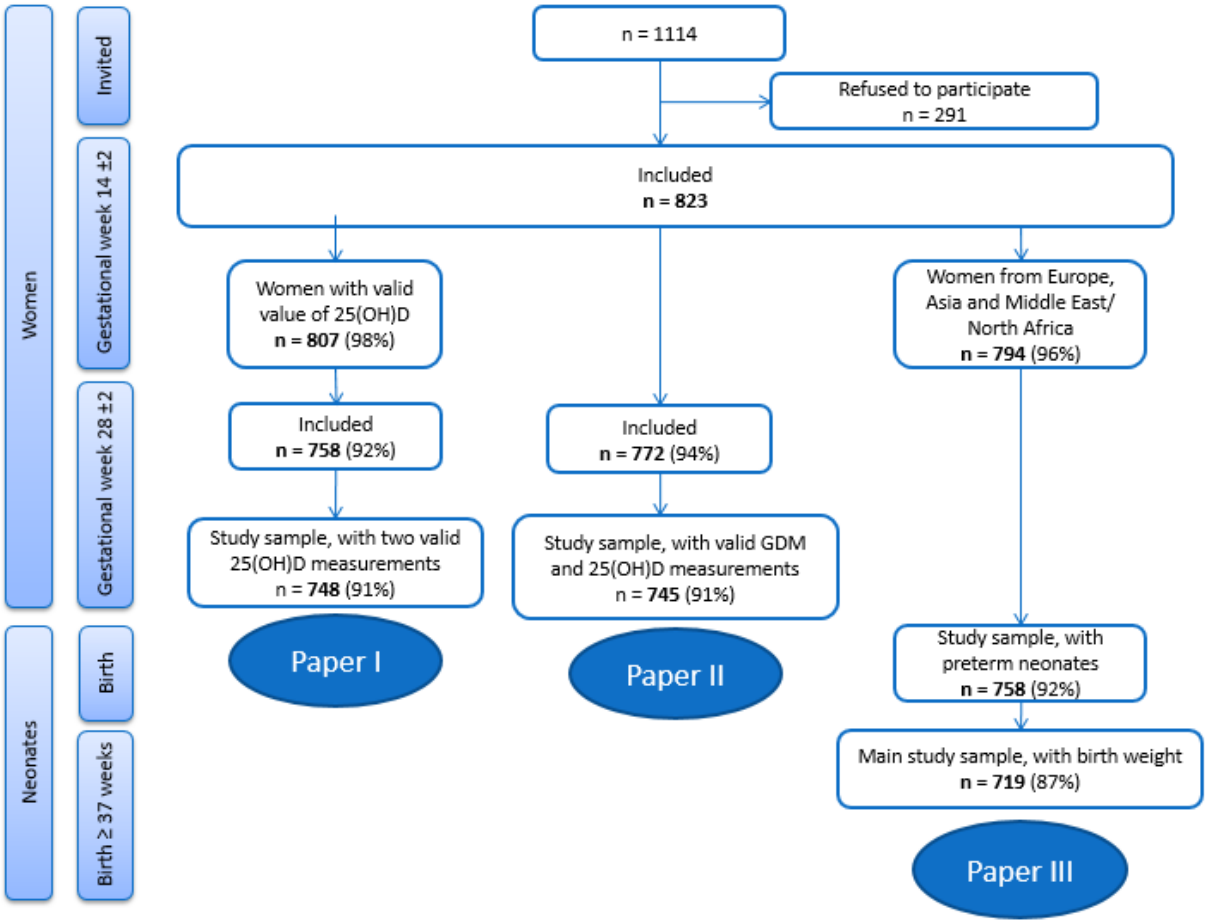
Study population and study sample

Of 1114 invited women, 823 were included in the study, resulting in a participation rate of 74% (ranged from 82% in Europeans, 71% in Asians, 65% in Middle Easterners to 64% in Africans) (185). In total, 59% of the included women were of ethnic minority background. In Paper I, the final sample of study participants comprised 748 women with two measurements of 25(OH)D levels (see the flow chart in Figure 3). In Paper II, the final sample of study participants comprised 745 women with valid GDM and 25(OH)D measurements (see the flow chart in Figure 3). In Paper III, the study sample with preterm neonates included 758 women and their neonates. The main sample of study participants, with birth weight, included 719 women and their neonates (see the flow chart in Figure 3). Overview of the papers is presented in the flow chart in Figure 3. For details, flow charts for each paper are presented in the Appendix.

Data collection

Maternal data from questionnaires, measurements and blood samples were collected at 15 and 28 weeks of gestation according to a detailed protocol. Study personnel were certified after extensive training, and study personnel (assisted by professional interpreters when needed) collected information through interviews. Specially trained and certified midwives performed clinical measurements for neonates at birth according to the study protocol.

Figure 3. Flow chart. Overview of study samples in Paper I-III



Recommendation of vitamin D supplementation

In accordance with our study plan and in line with ethics protocols, women with 25(OH)D values less than the laboratory's lower reference range (<37 nmol/L) at 15 and 28 gestational weeks (GWs) were provided with written information about their 25(OH)D levels, and a recommendation to consult their GP for treatment. The GPs were advised to prescribe 20 µg (800 IU)/day vitamin D_3 for 1–3 months if 25(OH)D ranged from 12–37 nmol/L, or 30 µg (1200 IU)/day for 3 months if 25(OH)D was <12 nmol/L. The daily dose was below the tolerable upper intake level (50 µg/d) (186). In addition, 1 g calcium per day was recommended for both groups.

Primary outcomes

Paper I: Serum-25(OH)D

The primary outcome of interest, 25(OH)D level, was analysed by competitive radioimmunoassay (DiaSorin, Stillwater, MN, USA) at the Hormone Laboratory, Oslo University Hospital, Aker. The method measures total 25(OH)D (both 25(OH)D_2 and -D_3), with intra- and inter-assay coefficients of variation of 6% and 13–16%, respectively. The laboratory is accredited by the International Organization for Standardization and is part of the Vitamin D Quality Assessment Scheme, DEQAS. Maternal 25(OH)D was analysed at 15 and 28 GWs, and 25(OH)D levels were the primary outcome variable (see Table 2 and Table 3). The lower limit for detectable 25(OH)D with the immunoassay method was 12 nmol/L, and concentrations of 25(OH)D (<12 nmol/L) were replaced with "11 nmol/L" in the calculations (n=17 in Paper I, n=16 in Paper II, n=17 in Paper III).

Paper II: Gestational diabetes

In Paper II, GDM was the primary outcome variable (see Table 2 and Table 3). A standard 75 g oral glucose tolerance test was performed at 28 GW (114) and venous blood glucose was measured on site with a plasma calibrated HemoCue 201+ (Angelholm, Sweden). During the study, women were diagnosed with GDM by the WHO_{1999} criteria (fasting plasma glucose (FPG) ≥7.0 or 2-hour plasma glucose (PG) ≥7.8 mmol/L) (102). In the paper, we reported GDM by the modified diagnostic criteria for GDM by the WHO_{2013} (FPG ≥5.1 or 2-hour glucose ≥8.5 mmol/L (1-hour glucose was not used as this variable was not collected) (107, 187).

Paper III: Neonatal anthropometric measures

In Paper III, offspring birth weight was the primary outcome variable (see Table 2 and Table 3). Hospital staff routinely measured the birth weight of all neonates immediately after delivery.

Secondary outcomes

Paper I: change in 25(OH)D

The secondary outcome was change in level of 25(OH)D between inclusion and 28 GW.

Paper II: FPG, 2-hour PG, fasting insulin, fasting C-peptide, HOMA-IR, HOMA-B

The secondary outcomes were the variables FPG, 2-hour PG, insulin resistance (measured by homeostatic model assessment of insulin resistance (HOMA-IR)), β-cell function (HOMA-B), and fasting serum insulin and C-peptide. Venous blood was sampled in the morning after an overnight fast at the follow-up visit at 28 GW. Insulin and C-peptide were measured at the Hormone Laboratory, Oslo University Hospital, by non-competitive immunofluorometric assays (DELFIA, PerkinElmer Life Sciences, Wallac Oy, Turku, Finland). Insulin resistance (HOMA-IR) and β-cell function (HOMA-B) were estimated by the Oxford University HOMA Calculator 2.2 with FPG and C-peptide concentrations (188). FPG values used in the calculations of homeostatic model were measured at the Akershus University Hospital from venous blood on gel tubes, (Vitros 5.1 FS, Ortho Clinical Diagnostics, slide adapted colorimetric method).

Paper III: crown-heel length, head circumference, abdominal circumference, sum of skin folds, mid-upper-arm circumference, ponderal index

Other neonatal anthropometric measures – crown-heel length, head circumference, abdominal circumference, sum of skin folds, mid-upper-arm circumference, ponderal index and SGA – were secondary outcome variables. Crown-heel length, head circumference, abdominal circumference, sum of skin folds and mid-upper-arm circumference were measured within 72 hours after birth for neonates born at term (gestational age ≥37 weeks), unless there were medical contraindications. Neonatal anthropometric measurements were performed by specially trained study personnel (136). "Sum of skin folds" was the sum of the triceps skin fold, the sub-scapular skin fold, the supra-iliac skin fold and the thigh skin fold. All measurements, except length, were performed twice (circumferences and length were measured to the nearest 0.1

cm, and skin folds to the nearest 0.1 mm) and calculated as the mean of two measurements. Mean values were used unless there was a difference of >0.5 cm for circumferences and >0.5 mm for skin folds, when a third measurement would be performed. Ponderal index was calculated as birth weight (kg)/crown-heel length (m^3) (136). Small for gestational age (SGA) was defined as <10th percentile according to the Norwegian national references (130).

Explanatory variables

Paper I: Ethnicity/geographic origin

Geographic origin/ethnicity was the explanatory variable of interest. Ethnicity was categorized into the following regions: Western Europe, South Asia, the Middle East/North Africa, South Sahara Africa, East Asia and Other (ethnic origin from Eastern Europe, and Central and South America due to the small sample size) (see Table 2).

Paper II and III: 25(OH)D – as a continuous and as a categorical variable

The explanatory variable of interest was 25(OH)D in Paper II and III. In Paper II, 25(OH)D was analysed as a continuous variable and dichotomized variable according to deficiency <50 nmol/L at 15 GW, and as a categorical variable, to reflect vitamin D status during pregnancy (see Table 2 and Table 3). In Paper III, maternal 25(OH)D was analysed as a continuous variable both at 15 and 28 GWs, and then as a categorical variable, (see Table 2 and Table 3). As treatment was recommended when 25(OH)D <37 nmol/L, we categorized 25(OH)D to reflect 25(OH)D levels during pregnancy. The variable used in Paper II and III was categorized as:

- *consistently sufficient level* (≥37 nmol/L at 15 and 28 GWs)
- *consistently deficient level* (<37 nmol/L at 15 and 28 GWs)
- *increasing level* (<37 nmol/L at 15 GW and ≥37 nmol/L at 28 GW)
- *decreasing level* (≥37 nmol/L at 15 GW and <37 nmol/L at 28 GW).

Confounding

Demographic and other variables related to pregnancy and birth

Paper I: Demographic variables (maternal age, parity, education level), gestational week at inclusion, season of blood test, use of vitamin D supplements and pre-pregnancy BMI *(Table 2 and Table 3).*

Demographic variables were as follows: Maternal age was calculated according to the day of inclusion. Maternal birth dates were cross-checked with maternal child health clinic records which are linked with the Norwegian population register. Parity was defined as number of previous pregnancies lasting more than 22 weeks, and categorized as no children (nulliparous), one child (uniparous) and two or more children (multiparous). Education level was categorized as <10 years, 10–12 years (high school education) and >12 years (college/university education).

Variables related to pregnancy: Gestational week at inclusion (derived from the first day of the woman's last menstrual period) was dichotomized according to the median because of non-linearity. Winter season was defined as December to May, and summer season as June to November on the basis of seasonal variations in 25(OH)D levels. According to the National Clinical Guidelines for Antenatal Care, the recommended vitamin D intake during normal pregnancy is 10 μg/day (189). At both visits, all participants were asked about their intake of vitamin D supplements during the past two weeks, and the self-reported intake was categorized as "vitamin D ≥10 μg/day" or "no or vitamin D <10 μg/day". Pre-pregnancy BMI (calculated from self-reported weight before pregnancy and height objectively measured to the nearest 0.1 cm by using a fixed stadiometer at inclusion) was categorized as <25 kg/m^2 or ≥25 kg/m^2.

Paper II: Demographic variables (ethnicity, maternal age, parity, education level), season of blood test, sum of maternal skin folds and change in sum of skin folds *(Table 2 and Table 3).*

The demographic variables were as described for Paper I, but also covered ethnicity. Maternal ethnicity was categorized into geographic origin: from Europe, South Asia,

Middle East/North Africa, South Sahara Africa, East Asia (see Table 2). Because of the small numbers of participants from South and Central America, these women were excluded from the analyses.

Variables related to pregnancy: Season for 25(OH)D measurements at 15 GW was defined as winter (December to May) and summer (June to November). Specially trained study personnel at 15 and 28 GW performed maternal anthropometric measures. "Sum of skin folds" was the sum of the triceps skin fold, the sub-scapular skin fold and the supra-iliac skin fold. All measurements were performed twice (to the nearest 0.1 mm), and calculated as the mean of two measurements. Mean values were used unless there was a difference of >0.5 mm for skin folds, when a third measurement would be performed. Change in "sum of skin folds" were calculated as the difference between "sum of skin folds" at 15 and 28 GW. Pre-pregnancy BMI was used as a continuous variable, and weight gain was calculated as the difference between pre-pregnancy weight and weight at 28 GW.

Paper III: Demographic variables (ethnicity, maternal age, parity, education level), neonate gender, gestational week at birth, season at birth, and pre-pregnancy BMI *(Table 2 and Table 3).*

The demographic variables were as described for Paper I, but also covered ethnicity. Maternal and offspring ethnicity was categorized into geographic origin: from Europe, Asia or Middle East/North Africa including Horn of Africa (see Table 2). Because of the small numbers of participants from South and Central America and other African countries, these women and neonates were excluded from the analyses.

Variables related to birth: Gestational week at birth, derived from the first day of the woman's last menstrual period, was used as a continuous covariate. Season at birth was categorized in groups: summer from June to August, autumn from September to November, winter from December to February and spring from March to May.

Statistical analyses

All statistical analyses were performed using SPSS software version 22 and Stata/SE 14.1. Explanatory linear regression model analyses were performed to assess the

relationship between ethnicity and the concentration of 25(OH)D, both at inclusion and at 28 GW (Paper I).

Logistic regression models were performed to assess the relationship between 25(OH)D and GDM (Paper II). Separate generalized linear models were performed to assess the relationship between 25(OH)D and each of the following outcomes: FPG, insulin, C-peptide and HOMA-IR (Paper II).

Separate generalized linear models were performed to assess the relationship between 25(OH)D and each of the following outcomes: birthweight, crown-heel length, head circumference, abdominal circumference, sum of skin folds, mid-upper-arm circumference and ponderal index (Paper III). Generalized logistic regression models were performed to assess the relationship between 25(OH)D and SGA as the outcome (Paper III).

Ethics

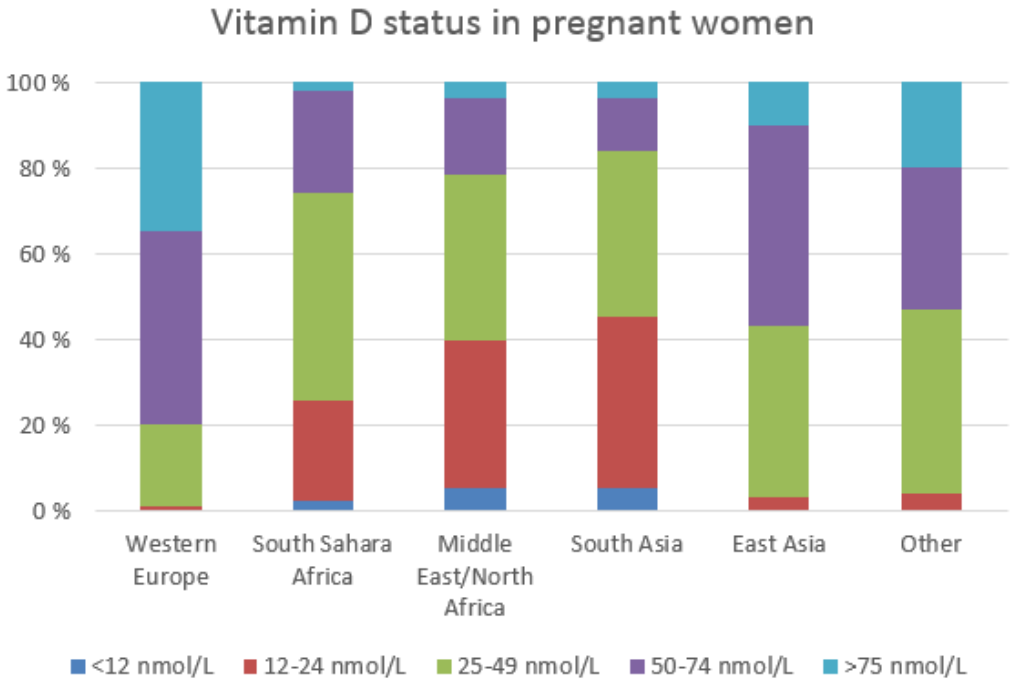
The Regional Committee for Medical and Health Research Ethics for South-Eastern Norway (REK 2007/894 and REK 2015/1035C) and the Norwegian Data Inspectorate approved the study protocol. Participation was based on informed, written consent from each woman on behalf of herself and her offspring. The fathers gave separate written informed consent. The study was conducted in agreement with the Helsinki Declaration. Personal identifying information was removed from all data prior to analyses.

SUMMARY OF RESULTS

Paper I

Vitamin D deficiency was very prevalent in women with ethnicity from South Asia (84%), the Middle East (79%), South Sahara Africa (75%) and East Asia (43%), compared with those from Western Europe (20%), ($p<0.01$) (Figure 4). Severe deficiency was found at 15 gestational week in 45% of women from South Asia, 40% from the Middle East and 26% from South Sahara Africa, compared with 2.5% in women from East Asia and 1.3% of women from Western Europe.

Figure 4. Proportions of participants (%) in categories of serum 25(OH)D concentrations in pregnant women at gestational week 15 according to geographic origin.

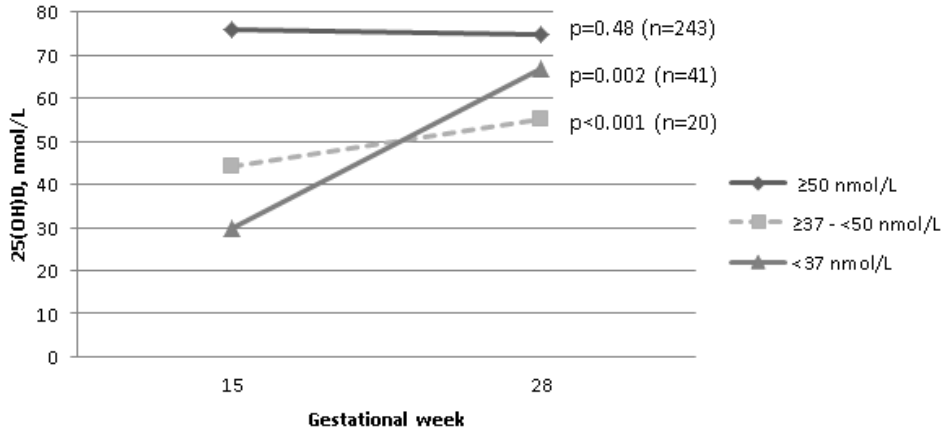


Women from South Asia, the Middle East and South Sahara Africa had mean values that were 20–28 nmol/L lower than in Western women after adjusting for age, parity, season, education and intake of vitamin D supplements. Ethnicity, education, season and intake of vitamin D were independently associated with 25(OH)D ($p<0.01$). The effect of season on 25(OH)D differed by ethnicity (interaction term, $p<0.01$). Western European women had a higher concentration of 25(OH)D during summer compared with winter, while no seasonal difference was observed among ethnic minority women, and their mean values were lower than those for Western Europeans.

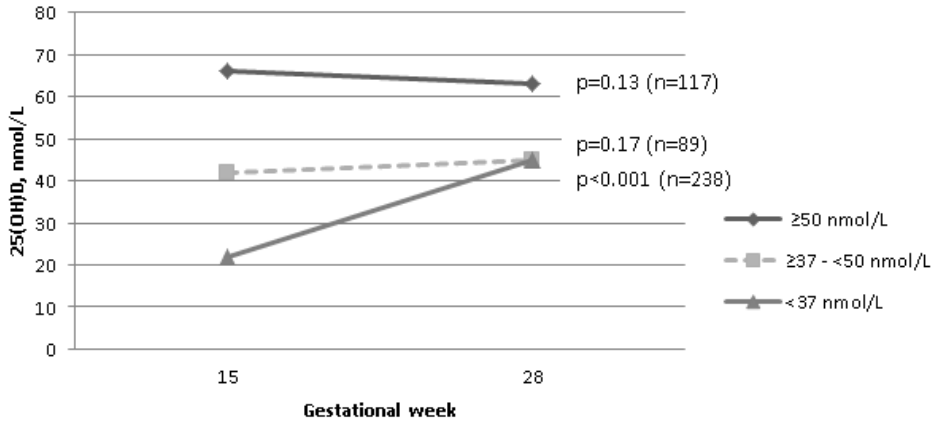
In total, 35% of the women had 25(OH)D values <37 nmol/L at inclusion and were recommended to consult their GPs for the prescription of supplements. Only 37% of these women initially reported an intake of ≥10 μg/day of vitamin D supplements, but at 28 gestational week, this proportion had increased to 73% (p<0.01). At 28 gestational week, the mean 25(OH)D had increased from 23 to 47 nmol/L (p<0.01) in women who were recommended vitamin D supplementation, with small or no changes in women with sufficient vitamin D levels at baseline (Figure 5).

Figure 5. Mean 25(OH)D levels at gestational weeks 15 and 28 – stratified for baseline levels.

Western European women:



Ethnic minority women:



Paper II

Among women with GDM, 60% had vitamin D deficiency (25(OH)D <50 nmol/L) compared with 49% among non-GDM women (p<0.01). A higher proportion of ethnic minority women had GDM (Figure 6) compared with European women. Ethnic minority women had lower mean 25(OH)D compared with European women (Figure 7).

Figure 6. Ethnic variation in gestational diabetes (GDM).

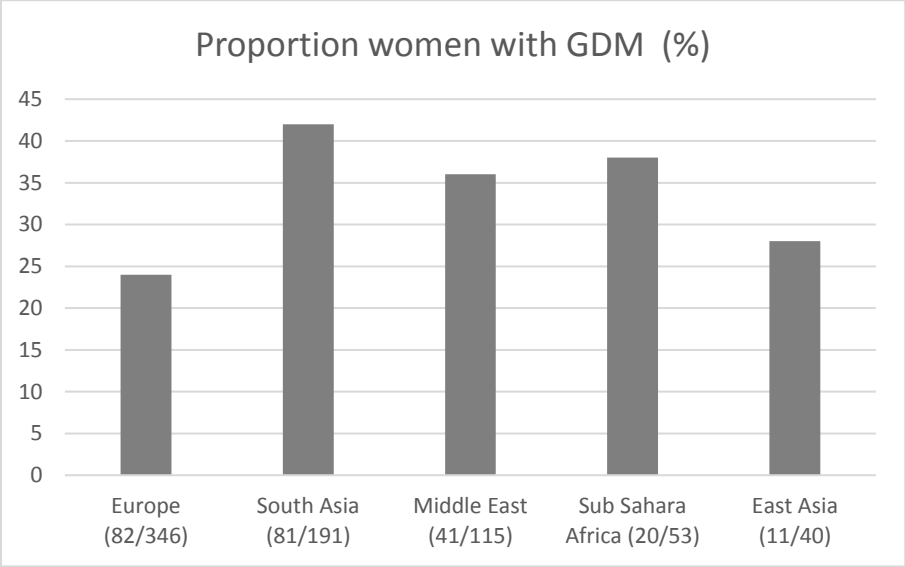
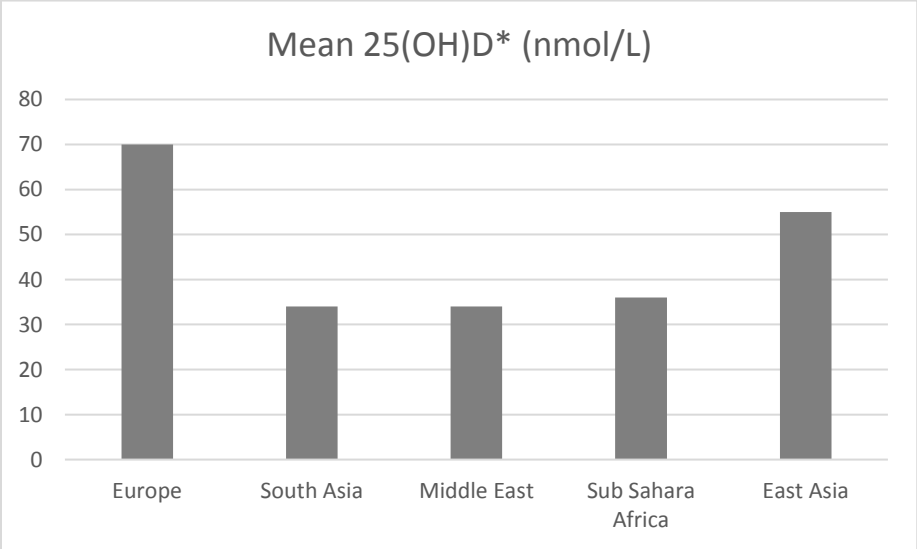


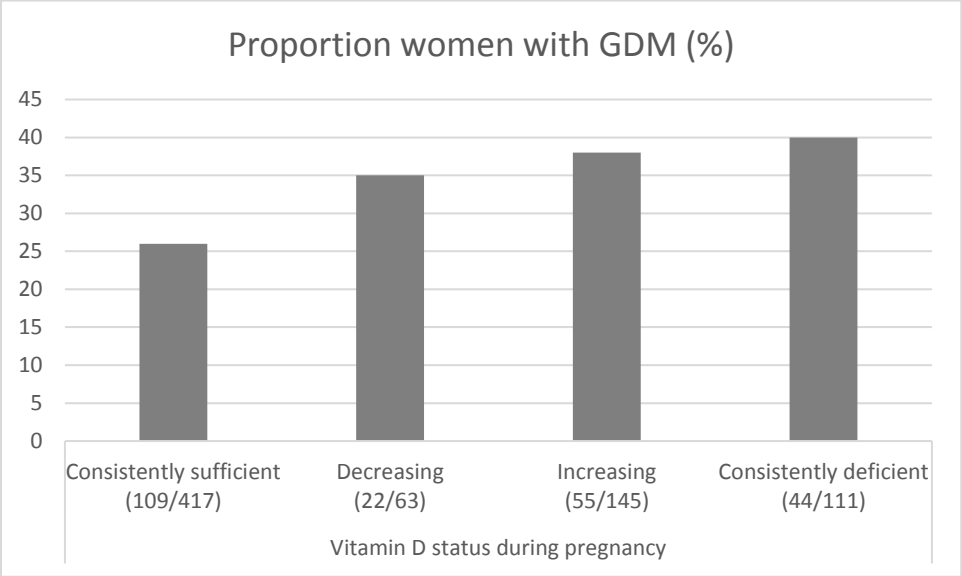
Figure 7. Ethnic variation in serum 25(OH)D concentrations.



25(OH)D: 25-hydroxyvitamin D; *15 gestational week

Using categories of 25(OH)D reflecting vitamin D status during the first 28 weeks of gestation, a higher proportion of vitamin D deficient women had GDM (40%) compared with women with consistently sufficient level (26%) ($p<0.01$) (Figure 8).

Figure 8. Proportion women with gestational diabetes (GDM).



In univariate analyses, 25(OH)D <50 nmol/L at inclusion was associated with GDM, and also after adjusting for maternal age, parity, education level and season (OR 1.6, 95% CI 1.1-2.2). After adjusting for variables reflecting fat mass ("sum of skin folds" at inclusion and change in "sum of skin folds"), OR was slightly reduced and the association was no longer significant. After additionally adjusting for ethnicity, the OR was even more attenuated. We found similar results with no association between GDM and vitamin D status reflecting the 25(OH)D level throughout pregnancy, using the categorized variable. In a sensitivity analyses, we found similar results using pre-pregnant BMI and weight gain instead of measures of skin folds.

At 28 gestational week, significant inverse correlations were found between 25(OH)D in early pregnancy and measures related to insulin resistance (FPG, HOMA-IR, fasting insulin and C-peptide), but not with insulin secretion (HOMA-B) or 2-hour PG. We found no independent association between 25(OH)D and FPG, HOMA-IR, fasting insulin and C-peptide after similar adjustments. All significant associations disappeared after adjustments for confounders, with ethnicity having a stronger effect on the estimates than the adiposity variables.

Paper III

Mean birth weight was 3485 g, but differed according to ethnic group ($p<0.01$): 3623 g for European, 3455 g for Middle Eastern and 3286 g for Asian neonates. Maternal 25(OH)D at inclusion was positively associated with birth weight in univariate analyses, and also after adjusting for maternal age, parity, education level, pre-pregnancy BMI, gestational age, season and neonate gender ($p<0.01$). However, after additional adjustment for ethnicity, 25(OH)D level was no longer associated with birth weight. Similar results were found for the association between birth weight and the 25(OH)D level at 28 gestational week, or using the categorized variable reflecting 25(OH)D level throughout pregnancy (consistently low, consistently high, increasing or decreasing level). Further, as regards the association between 25(OH)D level and SGA as the outcome, no association was present after adjusting for ethnicity.

In univariate analyses and in models adjusting for maternal age, parity, education, pre-pregnancy BMI, gestational age, season and neonate gender, maternal 25(OH)D level was significantly associated with head circumference, abdominal circumference and ponderal index ($p<0.05$ for all), both when used as a continuous variable and as a categorized variable. However, after adjusting for ethnicity, 25(OH)D level was no longer associated with any of the outcomes. Gender-specific associations for abdominal circumference and sum of skin folds were found ($p<0.05$ for the interaction term).

DISCUSSION

Main findings

The main findings from the studies included in this thesis are:

- Paper I: Vitamin D deficiency was prevalent (75–84%) among South Asian, Middle Eastern and African women in early pregnancy, compared with 20% among Western European women. Of ethnic minority women, 26–45% had severe deficiency. Women from South Asia, the Middle East and Africa had mean values that were 20–28 nmol/L lower than in women from Western Europe. The serum levels of 25(OH)D increased significantly by 24 nmol/L from 15 to 28 gestational weeks in vitamin D-deficient women who received a recommendation for supplementation.
- Paper II: Despite associations between vitamin D and GDM or other measures of glucose metabolism in unadjusted analyses, we found no independent associations between vitamin D levels and the outcomes in this multi-ethnic cohort of pregnant women with a high prevalence of GDM and vitamin D deficiency. These results were consistent, irrespective of whether 25(OH)D levels were measured at 15 gestational week or whether changes in 25(OH)D levels between these time points were used in the analyses. The association between vitamin D and GDM in unadjusted analyses disappeared after adjusting for confounders, with ethnicity having a stronger effect than the adiposity variables.
- Paper III: We found no independent associations between maternal vitamin D levels and birth weight, crown-heel length, head circumference, abdominal circumference, mid-upper-arm circumference, sum of skin folds and ponderal index in this cohort of pregnant women with a high prevalence of vitamin D deficiency. These results were consistent, irrespective of whether 25(OH)D levels were measured in 15 or 28 gestational week, or whether changes in 25(OH)D levels were observed between these time points. The strong

association between ethnicity and neonatal outcomes was not affected by maternal 25(OH)D levels.

The studies have some limitations, which are addressed in detail in each paper, as well as in the following section.

Methodological considerations

Study design

The STORK Groruddalen Study is a longitudinal population-based cohort study following pregnant women and their offspring from early gestation to three months postpartum. We used both a cross-sectional (Paper I) and a cohort design (Papers I, II and III) in this thesis.

The descriptive, cross-sectional design used in Paper I provided new knowledge of the prevalence of vitamin D deficiency in early pregnancy among pregnant women living in Oslo. The major strength of a cross-sectional design is the ability to provide information about prevalence in a population at a relatively low cost (190). The design can also provide information regarding associations between exposures and outcome, but the main limitation of a cross-sectional study is related to the lack of causal inferences (190), although significant associations may represent risk factors for the outcome. If an association is found, further studies with a stronger design are necessary to assess causation. Further, even when an effect is observed in large samples, the effect size and clinical importance should be evaluated for any statistically significant result.

The population-based STORK Groruddalen study can provide information about the whole population with minimized selection bias, if found representative of the source population. To assess factors associated with vitamin D status at 15 and 28 weeks of gestation, and factors associated with maternal and neonatal outcomes, we used information of pre-pregnant status and data from early gestation in this cohort. The major strength of a cohort study is the prospective design, with exposures assessed before the outcomes (190). We used the prospectively collected information to explore factors associated with vitamin D deficiency (Paper I), GDM and glucose metabolism

(Paper II) and neonatal anthropometric measurements (Paper III). However, the presence of random errors, systematic errors and confounding in observational studies will always influence the results (190). To identify a definite causal relationship, a randomized controlled design is the gold standard.

However, causal inferences may be assumed also in observational studies. According to Bradford Hill, an English epidemiologist, a set of criteria can be used to provide evidence of a possible causal relationship between a cause and an effect (191).

The Bradford Hill criteria for causation are as follows:

- Strength of the effect size
- Consistency (reproducibility of different persons in different places with different samples)
- Specificity (specific association between a factor and an effect)
- Temporality (the effect must occur after the cause)
- Biological gradient (dose/response)
- Plausibility (mechanism between cause and effect)
- Coherence (between epidemiological and laboratory findings)
- Experiment
- Analogy (the effect of similar factors may be considered)

In addition, in modern epidemiology, new methods of exploring causality have been developed. Among these are use of the directed acyclic graph (DAG), which is a graphical display of causal relations among variables, developed to control for confounding factors (191). We used DAGs to examine the association between 25(OH)D levels (exposure) and 1) GDM (outcome in Paper II) (Figure 9) and 2) birth weight (outcome in Paper III) (Figure 10). The one-way horizontal arrow indicates an acyclic direction of the exposure of interest on the outcome. The other arrows indicate the influence of other confounding factors on the exposure and the outcome. Using a DAG will help in the statistical analyses to only adjust for confounders.

Figure 9. DAG of causal relationships between maternal 25(OH)D levels and gestational diabetes (GDM).

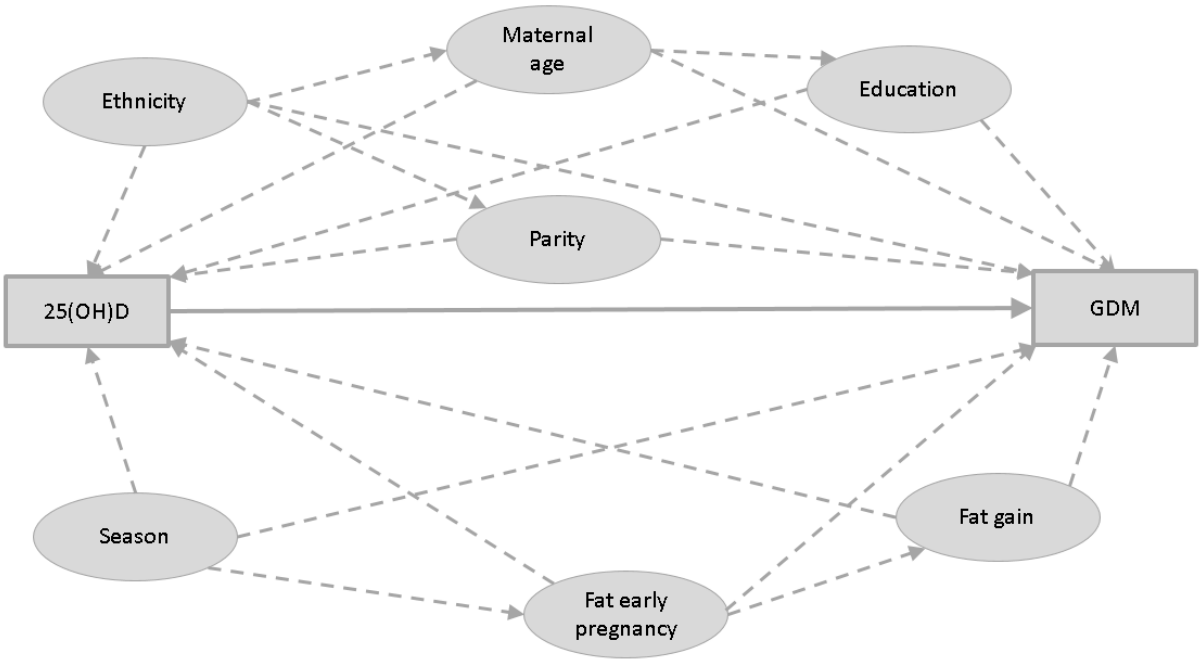
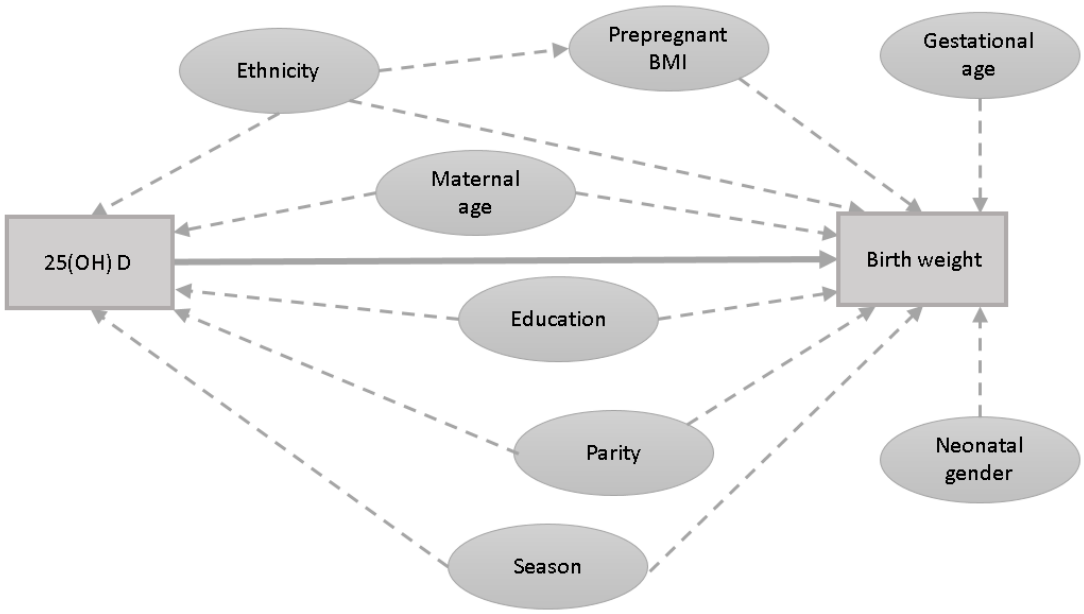


Figure 10. DAG of causal relationships between maternal 25(OH)D levels and birth weight



Random errors and reliability

Random errors are due to chance and appear if inaccuracy of the measurements (exposures and/or outcomes) exist or if the sample size is low. Reliability refers to the degree to which the results can be repeated under identical conditions (191).

By increasing the sample size, the influence of random errors can be reduced, and the precision of the effect estimates increases. Our focus has been on the largest minority groups from South Asia and the Middle East. In Paper II, we excluded Central and South America, and in Paper III, we excluded South Sahara Africa, and Central and South America because of the heterogeneity of origin and the small sample size.

Both random and systematic errors may cause biased estimates (190).

Systematic errors and internal validity

Internal validity refers to the degree of bias (systematic errors) in the way the data are collected, analysed and interpreted in a study (190). Internal validity depends on the methods used to select the study subjects, collect the relevant information and conduct the analyses (191). However, being aware of potential bias will help us to interpret the results more correctly. A common classification of bias is selection bias, information bias and confounding, and I will discuss each of these in the following sections.

Selection bias

Selection bias concerns the study participants' representativeness in relation to the source population, and is related to procedures used to select study participants (190).

We do not consider that selection bias had a major impact on the results:

- The study population (n=823) of pregnant women was found to be representative of the source population regarding ethnicity and age, although a higher proportion of parous South Asian women declined to participate (185). Of the 804 women not eligible and the 291 who refused to participate, there was a slight selection bias towards lower parity among South Asians and lower age among Africans in the study population compared with those not included (Flow chart for the STORK Groruddalen study, Appendix (185)).

- In Paper I, the study sample was selected based on two repeated measurements of 25(OH)D levels. No significant differences between the study sample and the 75 excluded women were found for ethnicity, age, gestational week, parity, pre-pregnant BMI or education.
- In Paper II, the study sample was selected based on measurements of FPG and 2-hour PG for the diagnosis of GDM. No significant differences between the study sample and the 78 excluded women were found for baseline characteristics (ethnicity, age, parity, pre-pregnant BMI or education) (114). Other measures of glucose metabolism were obtained from a slightly lower number of women (n=731, subsamples).
- In Paper III, the study sample was selected based on measurements of birth weight. The study sample seems representative for the women included in the study population. No significant differences between the study sample and the 104 excluded women were found for ethnicity, age, gestational week, parity, pre-pregnant BMI or education.
- We cannot rule out a selection bias, as anthropometric data of the newborns were obtained from a lower number of neonates (subsamples). However, eligible neonates without study-specific measurements were considered missed at random because of logistic problems at the hospitals, and mothers without study-specific anthropometric measurements (birth weight) of their neonates were comparable to mothers with measurements of their neonates for all factors: 25(OH)D, ethnicity, age, gestational week, parity, education and pre-pregnancy BMI (136).
- We have reduced selection bias by not excluding preterm neonates in the analyses of SGA, as low 25(OH)D status may induce preterm birth. A selection of only term neonates could have introduced bias, and thereby given an underestimation of an association between maternal 25(OH)D levels and SGA. At a population level, usually only term births (≥37 weeks of gestation) are included in studies evaluating birth weight as a measure of foetal growth (192). We wanted to focus on foetal growth using healthy neonates, and therefore we

excluded preterm births in the analyses of birth weight and other anthropometric measures.

Information bias

Information bias occurs when exposure and/or outcomes are measured with measurement errors (190). Measurement errors may be objective measurement errors or misclassification of self-reported information or objective measurements (191). Recall bias (completeness of recall to memory of past events/experiences) and desirability bias (over- or underestimation) may create bias in self-reported information (191).

Bilingual translators were used to reduce bias as information that is more correct could be obtained when language barriers were reduced. Furthermore, a more representative sample of the source population could be recruited. We used information from questionnaires and objective measurements. Most of the questions had been validated or used in other studies, but not all translated versions had been formally validated by forward-backward translation due to resource limitations. We cannot exclude information bias, as not all questions were checked for cross-cultural validity.

In the following, I will discuss information bias in further detail.

- *Measurement of 25(OH)D levels*

  We assume low probability of information bias regarding measurement of 25(OH)D levels as the analyses were reliable and valid. In all three papers, 25(OH)D levels were analysed at the same laboratory, the Hormone Laboratory, Oslo University Hospital, using the immunoassay method. Cashman et al. re-analysed 25(OH)D data from four Nordic population samples using LC-MS/MS and comparing results from the immunoassay methods with the gold standard method; the results from the Hormone Laboratory were only modestly changed (+1.4 nmol/L) (10). This indicates that the analyses of 25(OH)D levels are reliable and valid with few measurement errors. In addition, we do not assume that the replacement of 11 nmol/L in the

calculations has biased our findings, as only a very few individuals had undetectable values by this method.

- *Ethnicity and geographic region*

  Merging different ethnic groups by geographic regions or geographic origin should be done with caution, as heterogeneity within a group may exist, and misclassification of ethnicity can create bias depending on which aspects of ethnicity one intends to measure (118). We merged country of origin with geographical regions because of small numbers of participants for most countries, despite a possible neutralizing effect if there was heterogeneity within the larger groups. However, despite some cultural differences such as clothing and diet, we consider that information bias had a minor impact on the results as the geographical regions are at approximately the same latitude with intercultural exchange, including shared genetics relevant for vitamin D metabolism, over the centuries.

- *GDM diagnosis and maternal glucose measurements*

  The HemoCue method used to measure glucose, has been authorized by the Food and Drug Administration (Department of Health and Human Services, USA, 2002) to diagnose diabetes, and for use in epidemiological research (187). The HemoCue instruments at the three maternal child health clinics were calibrated for plasma and were externally validated one to two times per year, in addition to the weekly quality checks according to specifications from the manufacturer and the study protocol (187). The HemoCue method was preferred for practical reasons, as women could be directly informed about their diagnosis at the same visit, and to avoid pre-analytical glycolysis during shipment to the laboratory (187). The on-side measured plasma glucose values were checked in a subgroup of samples against the serum glucose values measured by standard clinical chemistry laboratory (Akershus University Hospital), and the correlation between these two measurements were high

(187). This indicates that the analyses of FPG and 2-hour PG levels are reliable and valid with little measurement error.

GDM diagnosis: As the IADPSG criteria were published later, the study lacks the 1-hour PG value included in the IADPSG criteria. The proportion of women identified with the 1-hour PG value only, is difficult to estimate. However, the majority of women with GDM by the IADPSG criteria are diagnosed based on the fasting glucose value (113, 187). Therefore, we assume little impact of information bias regarding lack of 1-hour PG values.

Other measures of glucose metabolism: The HOMA index estimates insulin resistance and β-cell function from a mathematical model based on FPG and fasting C-peptide values. The HOMA indices have been validated and used in studies of pregnant women (193). As they are estimated from fasting values only, these surrogate measures are appropriate for epidemiological studies. However, the correlation of HOMA against gold standard methods differs. In addition, HOMA-B has limited ability to detect chronic β-cell dysfunction because it assesses insulin secretion in the fasting state only and not the response over time after a glucose load. Regarding insulin resistance, we assume information bias have a minor impact on the results as FPG was valid and reliable, and C-peptide was measured at the accredited Hormone laboratory.

- *Neonatal anthropometric measurements*

Birth weight: We assume a low probability of information bias regarding measurement of neonatal birth weight. Before study start, study staff checked the scales by weighing a 3 kg item on all scales in both hospitals and the maximum difference observed between the scales was 5 g. Hospital staff regularly calibrated scales for measurement of birth weight to avoid systematic errors.

Other anthropometric measures: We cannot exclude information biases for every neonatal outcome, although we consider that information bias had a minor impact on the estimates, as the reliability was good regarding the anthropometric measures, except for mid-upper-arm circumference (Paper III) (136). *The inter-rater reliability* is the degree of stability exhibited when a measurement is repeated under identical conditions by different persons (191). The inter-rater reliability was high and assessed biannually; the inter-rater reliability between study personnel was in the range of 0.9–1.8% regarding length, head circumference, and abdominal circumference, while it was in the range of 8–13% for skin folds (136). *The intra-rater reliability* is the degree of stability exhibited when a measurement is repeated by the same persons on different occasions (191). The intra-rater variability was less than 5% in all measurements for all study midwives.

SGA: We used the standard for SGA of a Norwegian population of neonates, which may lead to more Asians diagnosed as SGA, as the mean birth weight of Asian neonates is considerably lower than that of European neonates (132, 133). Thus, we cannot exclude misclassification with an overestimation of SGA in the Asian neonates.

In the following, I will discuss information bias regarding factors we used for adjustments.

- *Season of 25(OH)D measurements*

  The dichotomization of season in Papers I and II could bias the results, as September, October and November were included in the summer season, even though the concentration of 25(OH)D decreases during this period. However, we consider that misclassification, if present, had a minor impact on the results, as 25(OH)D levels were still above 50 nmol/L in the autumn months. We chose to dichotomize season according to relevant literature to facilitate comparison (31, 194).

- *Vitamin D supplementation*

  To reduce the risk of recall bias, we asked about intake of vitamin D supplements during the previous two weeks instead of a longer period. Detailed information of daily intake was obtained to reduce social desirability bias. However, if the intake dose was more than 10 μg/day, the dose was not specified in most cases, and could have been higher. More specific data on intake in micrograms/day of vitamin D would have been valuable. To reduce misclassification of intake, we chose to dichotomize the intake of vitamin D supplements.

- *Calculation of gestational age*

  The first day of the woman's last menstrual period (LMP) was self-reported, and this information may be hampered by recall bias. To reduce bias, the ultrasound term was used when LMP was uncertain or when LMP differed by more than 14 days from the ultrasound term (195).

- *Categorization of season of birth*

  To reduce misclassification, season of birth was categorized into four seasons in Paper III.

- *Maternal anthropometric measurements*

  The self-reported pre-pregnant weight may be underestimated, implicating social desirability or recall bias. One study from Italy, the Netherlands and North America found that people underestimated their weight by 1.1 kg, and overestimated their height by 1.1 cm (196). We asked the women about their body weight prior to pregnancy shortly after being weighed, which probably reduced the risk of underestimation or overestimation. There was a strong correlation between pre-pregnant body weight and measured body weight, which indicates low misclassification of self-reported information and good internal validity (197). Regarding skin fold measurements, large measurement errors have been shown in other studies. Therefore, the inter-rater variability

was assessed biannually. The inter-rater variability was 7.4-24.7% and higher than recommended in studies on an individual level, but found to be acceptable on a group level, and the intra-rater variability was 5% or less. We assume the reliability was fairly good regarding the maternal anthropometric measures with minor impact on the estimates for the ethnic groups.

- *Education*

  Questions regarding information about education consisted of six alternatives, with detailed information required for number of years of completed schooling. We chose to categorize education into three levels, as this reduces misclassification of the detailed self-reported information. However, there may be some information bias regarding education as the content of education and the quality of the educational system varies widely in different cultures and geographic regions.

- *Age*

  On arrival in Norway, the year of birth is decided based on information supplied by the immigrant. We have no reason to assume that this information is biased across ethnic groups.

- *Parity*

  We have no reason to assume that the information about parity should be over- or underreported causing bias of this information. The greatest effect of parity on neonatal outcomes is reported between the first and the second child (198), and we have categorized parity into three groups, reducing the probability of misclassification.

Confounding

Confounding is a biased effect estimate of an exposure on an outcome because of the presence of common causes of the exposure and the outcome (191). Confounding will always be present in observational studies (190). By adjusting for potential confounders, the results will be more correct, although there will always be a risk of

residual confounding. The risk of over-adjusting also exists; adjusting for factors that are not confounders may introduce bias and falsely affect the results (190).

The pathways that may explain differences in 25(OH)D levels according to ethnicity or geographic origin are not straightforward as no confounder directly affects ethnicity. As there is no real confounder to ethnicity by definition, we examined the influence of variables as explanatory factors. In addition, we assume that some of the effect of geographic origin/ethnicity (exposure) on 25(OH)D levels (outcome) primarily acts through intermediate factors.

Unfortunately, information about vitamin D in the diet, clothing habits, travelling to lower latitudes and sun exposure were not available, and residual confounding may be present (Paper I). The residual confounding would probably not be the same for all the ethnic groups as the exposure to sun, diet including supplements and clothing differ between ethnic groups. How this residual confounding affects the estimates is unknown.

We used an explanatory model with 25(OH)D level as the exposure variable and GDM as the outcome (Paper II). We drew a DAG prior to the regression analyses (Figure 9). In this model, we adjusted for confounders affecting 25(OH)D levels and GDM. Similar, we used an explanatory model with 25(OH)D levels as the exposure variable and neonatal birth weight as the outcome in Paper III. We drew a DAG and adjusted for confounders affecting 25(OH)D levels and the neonatal birth outcomes (Figure 10). We also adjusted for two clinical variables (gender and gestational week) although not confounders.

External validity

External validity is the generalizability of the study results to subjects outside the study sample (190).

A majority (75-85%) of pregnant women in the study district attend the maternal child health clinics for antenatal care (185). The population-based design strengthens the external validity of the findings. Of the 1918 pregnant women attending maternal child health clinics in Groruddalen, 1114 (58%) were invited to the study, and of these, 291

(26%) refused to participate (Flow chart for the STORK Groruddalen study, Appendix (185)). Of the 804 (42%) women not invited, late attendance was the main reason. The study population was found fairly representative of the women attending maternal child health clinics regarding ethnicity, age and parity, although among women not included, the parity was slightly higher in South Asians and the age was slightly higher in Africans. The participating rate was 74%, with a range of 64–83% for ethnic groups, which is considered good in populations with a high proportion of hard-to-reach groups (113, 187). The 26% who did not participate in the study still attended the maternal child health clinics. However, probably some women in the district may have never attended the maternal child health clinics during pregnancy for various reasons (follow-up by a gynaecologist, the GP or intensive care in hospital), although this number is estimated to be very low.

The ethnicity of the source population was reflected in the study population and was thereby representative of the main ethnic groups of pregnant women living in Groruddalen (185). The samples in Paper I-III were representative for women included in the STORK Groruddalen study. Based on this, we assume that the generalizability of the 25(OH)D status in early pregnancy to pregnant women from the main ethnic groups in Oslo, and probably Norway, is relatively good. However, the generalizability for 25(OH)D status is lower in gestational week 28, as detailed recommendations about vitamin D supplements were given to both the women and their GPs for ethical reasons. In addition, we assume that the generalizability of findings for GDM and other measures of glucose metabolism of pregnant women living in Oslo is fairly good (187). We also assume that the generalizability of birth weight and the other anthropometric measurements of neonates to the main ethnic groups living in Oslo is fairly good (136). The results are probably generalizable to immigrants of similar ethnicity in other Western countries.

Discussion of main findings

Prevalence of vitamin D deficiency

Our results add important knowledge about vitamin D status in pregnancy in ethnic Norwegians as well as in ethnic minority groups in Norway where such information has been lacking. Our result of widespread vitamin D deficiency in pregnancy among ethnic minority groups is in line with studies of other ethnic groups from Europe and worldwide (74, 77, 79). We found a high prevalence of severe vitamin D deficiency among pregnant women with ethnic origin from Asia and Africa living in Oslo. This is in accordance with other studies of non-pregnant from Norway, although most other studies are smaller and encompass other ethnic groups (30, 32, 58, 84). However, an even higher prevalence of vitamin D deficiency and severe deficiency have been found among ethnic minority groups living in Oslo (25, 30-32, 35, 84) and in Europe (4, 6). To which extent the discrepancy in prevalence of vitamin D deficiency in different groups can be explained by different analytical techniques, season of measurement, ethnicities, or results from promotion of vitamin D supplementation in Oslo during recent years, is unknown. Interestingly, we found East Asians to have a higher vitamin D status compared with the other ethnic minority groups, although still lower than among pregnant Western European women. This result is consistent with results from the Oslo Immigrant Health Study (25). Our population-based study of pregnant women with a relatively large sample size complements and extends the knowledge to more ethnic groups, contexts and clinical outcomes.

Factors associated with vitamin D status

Our result is consistent with those of previous studies that found lower use of supplements in ethnic minorities (77, 182, 199), and with the Oslo Immigrant Health Study report that use of cod liver oil supplements and intake of fatty fish were positively associated with vitamin D status (25). Furthermore, our results support that after a simple recommendation of vitamin D supplementation to women with low values, the proportion of women using supplements increased, and their measured 25(OH)D levels increased by 24 nmol/L during the next 13 weeks. This is considered a clinically important difference, although we did not have a control group, as we had

a pre-post design. Interestingly, a similar effect of a moderate dose of vitamin D supplement on measured 25(OH)D level have been found in trials, lending support to our results (96, 200).

Further, we found an interesting interaction between season and ethnicity. We found no other European studies reporting similar findings. We identified one study from the US testing for this interaction; however, no interaction was found (201). We found a seasonal variation in vitamin D status among Western Europeans, with the lowest concentration during late winter months, with no clear variation among the ethnic minority groups. Different habits related to sun exposure, clothing habits and skin colour may explain this difference in seasonal variation in 25(OH)D concentration.

Our study adds important knowledge, as length of education was positively associated with vitamin D status. Only a few other studies have explored this association and found similar trends (25, 182). We recently found that ethnic minority groups with a low level of education and women with poor Norwegian language proficiency were less likely to use folic acid supplements compared with Western European women before and during pregnancy (202). The same may relate to use of vitamin D supplements. This is in line with results from Ireland reporting pregnant ethnic minority women from the Middle East and Africa having insufficient knowledge about vitamin D and its dietary sources (77). Persistent low health literacy regarding vitamin D is of concern, as rickets was previously prevalent among ethnic minorities, although fewer children have been diagnosed in recent years (54, 203). Despite public health recommendations of daily vitamin D intake in general, and during pregnancy in particular, this health information has not resulted in achieved recommended daily intake for all, indicating extra barriers for some groups (13, 189, 204).

GDM, glucose metabolism and associations with vitamin D

Discrepancy between the insulin secretion and the body' insulin needs is the reason of imbalance of glucose metabolism in GDM as in diabetes in general (103). The causal factors of GDM are heterogeneous with both genetic and environmental factors involved. As genetics have not changed over a short time, the environmental factors are responsible for the increased prevalence of GDM worldwide. However, the role of

vitamin D in this context is not clear. The strong association between 25(OH)D and GDM that we observed before adjusting for adiposity measures/fat mass and ethnicity have been found in many observational studies (87-89, 118-120). Furthermore, different criteria for GDM diagnosis make comparisons between studies a challenge, but also different definitions of vitamin D deficiency and analytical methods for 25(OH)D measurements make comparison difficult (118-120). In addition, some studies have a low prevalence of vitamin D deficiency among the women included and most studies use either a cross-sectional or case-control/nested case-control design, compared with our population-based cohort with a very high prevalence of vitamin D deficiency (119, 120). We did not find any other studies reporting vitamin D levels during pregnancy based on measurements of 25(OH)D at two time points, and 25(OH)D was analysed at a laboratory with high reliability and validity (10).

Adjustment for confounders is an important issue in observational studies. Some studies did not adjust for any confounders at all, although most studies adjusted for age, BMI and some for season of blood drawn (87, 88, 119). However, in line with our results, several observational studies found no association after adjusting for confounders (126, 205, 206). As body fat and weight gain are risk factors for GDM (106, 207), and 25(OH)D have been associated with adiposity and BMI (208, 209), adjusting for fat mass/deposits as a confounder is essential exploring the association between 25(OH)D and GDM. However, BMI is not a good measure of body fat across populations as Asians have a body composition with more visceral and central fat and more fat per BMI unit compared with Western Europeans (210). Many of the other studies adjusted for BMI, some for pre-pregnant BMI and only two for weight gain (211, 212). Physiological changes during pregnancy affect BMI, with weight of the foetus and placenta in addition to increased body fluid and fat deposits. We therefore measured skinfolds of the pregnant women, in addition to BMI, at inclusion and at time of GDM diagnosis. We found that the association was still significant after adjusting for BMI and weight gain. However, the association attenuated and was no longer significant adjusting for sum of skin folds and change in sum of skin folds instead of BMI and weight gain. This probably reflect skin folds as a more direct

measure of fat deposits and might be a better measure of fat deposits, especially in multi-ethnic populations (197).

Of studies that found an association, only few adjusted for socioeconomic status and (demographic) ethnicity (205, 212-215). In our study, the association with 25(OH)D disappeared after adjusting for ethnicity. Ethnicity probably reflects many factors that may be related to vitamin D or GDM, but not necessarily to both. Life style factors like physical activity and diet are related to ethnicity and GDM, but not necessarily vitamin D (216). Factors associated with vitamin D status – skin pigmentation, sun exposure, concealing clothes – are associated with some ethnic groups, but not necessarily with GDM. In addition, genes involved in vitamin D metabolism or GDM, although probably not the same genes, could be differentially expressed in different ethnic groups. Ethnicity is therefore an important confounder, although the effects on the exposure and the outcome are probably mediated through different mechanisms. Ethnicity could represent cultural, social, genetic or other unmeasured factors, and in this context, ethnicity is therefore an important confounder.

Similar to results for GDM, before adjusting for fat deposits and ethnicity, we found a strong association between 25(OH)D level and measures of insulin resistance (FPG, HOMA-IR, insulin and C-peptide). This is in line with other studies although studies are fewer and most report only correlations, with inverse correlations between 25(OH)D and FPG, insulin and different measures of HOMA (206, 217, 218). In addition, few used a longitudinal design. After adjustments for confounders – including ethnicity – many associations between 25(OH)D and different measures of insulin resistance and β-cell function disappeared, although results are inconsistent (206, 211, 213, 218, 219).

Although our cohort study satisfies the temporality criteria and other studies confirm plausibility, a biological gradient and coherence between observed associations in epidemiological and animal experiments, we did not find any association between 25(OH)D and GDM in the final model. In addition, different studies report inconsistent results. According the Bradford Hill criteria for causation, we do no assume 25(OH)D to be an important causal factor in the pathogenesis of GDM.

Neonatal body composition and associations with maternal vitamin D

Complex mechanisms involving genetics and a wide range of environmental factors determine foetal growth, birth weight and neonatal body composition. The strong associations between maternal 25(OH)D levels and birth weight that we observed before we entered ethnicity into the analyses have been found in several studies; four systematic reviews of both observational studies and RCTs (meta-analyses) have found a positive association between maternal 25(OH)D level and birth weight (57, 89-91). However, seven cohort studies found no association between maternal 25(OH)D level and birth weight (124-127, 171, 220, 221) while three found an association (194, 222, 223). In addition, previous meta-analyses of RCTs have indicated that vitamin D supplementation may increase birth weight (57, 89, 91, 224) and reduce the risk of low birth weight (87, 89, 90). However, a recent Cochrane review (75) with a meta-analyses based on five RCTs (225-229), reported no significant effect of vitamin D supplementation on birth weight.

After adjusting for ethnicity, the association between maternal 25(OH)D level and birth weight disappeared in our study. Only four other cohorts have studied this relationship in a multi-ethnic population, and none has included the same ethnicities as in our study. In two of these studies, an association was found between maternal vitamin D deficiency (respectively 25(OH)D <30 nmol/L and ≤25 nmol/L) and birth weight (194, 223), one with poorly defined ethnicity, making comparisons difficult (223). In addition, a large study from the Netherlands found a positive association between maternal 25(OH)D level and birth weight, length and head circumference, although not for foetal growth (222). However, only estimates for differences in z-scores were reported without unadjusted estimates, and a large number of maternal factors were adjusted for in the models, making comparisons between studies difficult.

One reason for the differences between our study and the two from the Netherlands could be residual confounding (194, 222). The biological effect of 25(OH)D could differ between the populations, as genotypes coding for proteins involved in the vitamin D metabolism may vary by ethnicity. Different genotypes coding for vitamin D binding protein, the vitamin D receptor and regulatory enzymes have been found in

ethnic groups, although results are inconclusive (145, 230-233). In addition, the ethnic and socio-economic composition of our sample differed somewhat from the two Dutch studies, which included Surinamese, Turkish, Moroccan, Cape Verdean and Dutch Antillean people. However, a multi-ethnic study of an Asian population found no association between maternal 25(OH)D level and birth weight, in line with our results (124). The prevalence of severe vitamin D deficiency was low, and our study with a high prevalence of severe deficiency complements their findings.

However, 25(OH)D levels may be more strongly associated with foetal growth restriction, such as SGA, than in normal foetal growth (234). Indirectly, SGA may induce preterm birth by elective C-section. In addition, low maternal levels of 25(OH)D have been associated with preterm birth directly, regardless of SGA. In contrast to other studies, we did not find any association between 25(OH)D level and SGA, although this result must be interpreted with caution (88, 194, 235).

Similar to results for birth weight, we found a strong association between maternal 25(OH)D level and head circumference, abdominal circumference and sum of skin folds before including ethnicity in the analyses, but all the associations disappeared after adjusting for ethnicity. Our findings are in line with other observational studies not finding any association between 25(OH)D level and length, head circumference, skin fold thickness and abdominal circumference (124, 127, 171, 220, 221). However, a few studies found an association between 25(OH)D level and length, head circumference (222), skin fold thickness, and circumferences (125, 126), while a study measuring body composition by dual energy x-ray absorptiometry (DXA) found a positive association between 25(OH)D level and offspring's fat mass at birth (128). In line with our study, a multi-ethnic study from Singapore found no association between maternal 25(OH)D level and any of the neonatal outcomes, including skin folds and abdominal circumference (124). In contrast to our findings and those from Singapore, a Cochrane review found some indication that maternal treatment with vitamin D supplements during pregnancy might increase infant length and head circumference at birth (75). We agree with the conclusion of the Cochrane review that further RCTs are required to confirm effects not found in most observational studies.

In sum, observational studies of neonatal anthropometric measurements do not support maternal vitamin D as a major environmental determinant of foetal growth, birth weight and body composition. A wide range of factors including maternal glucose and lipid levels and other micronutrients, maternal weight gain, physical activity and season as well as parental anthropometric measures and foetal gender regulate foetal growth (172, 236). These environmental factors may interact with each other, as well as with genetic factors. In addition, timing of exposure and setting (ethnicity, socio-economic status), plays a role for this complex interplay (172). In addition, the gender-specific associations regarding abdominal circumference and skin fold thickness in our study support maternal vitamin D as a possible environmental factor, in line with results from the studies from the Netherlands (194, 222). One study has found a positive association between maternal vitamin D status and fat mass at the ages of 4 and 6 years (128), and another study found that reduced concentration of maternal vitamin D was associated with reduced bone mass in children at 9 years of age (55). Additionally, in a case–control study, offspring of mothers with the lowest levels of 25(OH)D had more than twofold higher odds for type 1 diabetes compared with offspring of mothers with levels in the upper quartile in childhood (116). Further, we cannot exclude an effect of maternal vitamin D status on later disease in the offspring. However, the lack of effect in some longitudinal studies with proper adjustment for confounders, and also the inconsistency between studies regarding 25(OH)D and associations with neonatal anthropometric measures, does not support that vitamin D has an independent causal relationship with these outcomes, although a differential effect for subgroups (as gender) cannot be ruled out.

CONCLUSIONS

We have demonstrated a high prevalence of vitamin D deficiency among pregnant women in a multi-ethnic population, and severe deficiency in as much as 40% of women from Asia and Africa. A simple recommendation of vitamin D supplementation increased the vitamin D status significantly in pregnant women with low vitamin D status. Despite the high prevalence of maternal vitamin D deficiency, our results do not support an independent association between maternal 25(OH)D level and GDM, measures of maternal glucose metabolism including insulin resistance, nor neonatal body composition.

IMPLICATIONS

In our study vitamin D deficiency during pregnancy did not have an independent effect on GDM, but several systematic reviews and meta-analyses have found that vitamin D might play a role in glucose metabolism both in pregnancy and in general. Therefore, we cannot rule out vitamin D as an environmental factor also in the epidemiology of GDM and glucose metabolism. We support well-designed RCTs in multi-ethnic populations with low vitamin D status and high risk of GDM to determine the effect of vitamin D supplementation on prevention of GDM. Although vitamin D deficiency during pregnancy in our study and in other studies referred to above did not seem to affect birth weight, we cannot rule out other effects on the child. Developmental trajectories, both in growth and psycho-motoric development, may be affected by deficiencies during pregnancy. Further research regarding effects of maternal 25(OH)D levels on the foetus is required. Until we have evidence that maternal vitamin D level does not adversely affect the foetus regarding short and longer term outcomes, a more proactive attitude for treatment of maternal vitamin D deficiency may be appropriate. Similarly, because low vitamin D – 25(OH)D below 25 nmol/L – affects bone health, a more intensive treatment may be necessary in handling severe deficiency among children and adolescents still undergoing growth. In the meantime, we should prevent low levels of vitamin D during pregnancy and childhood. To do this, different interventions may work. Fortification, individual advice or increased

health literacy regarding vitamin D among ethnic minorities are different approaches. Ethnic minority women with less education are at risk and they should be targeted and receive tailored information on a healthy diet and supplement use.

Future perspectives

Large ongoing RCTs will hopefully give answers regarding causal relationships between low vitamin D status and CVD, cancers and total mortality. The first results are expected at the end of this year. In addition, waiting for more meta-analyses and systematic reviews of recent studies will also add valuable knowledge regarding adverse maternal and neonatal outcomes, in addition to long-term outcomes. Questions as to whether there are differences in the metabolism of vitamin D among different ethnic groups have been raised. Future research of ethnic differences in vitamin D binding protein, vitamin D receptor and regulatory enzymes, including differences in genotyping, is warranted as a high prevalence of vitamin D deficiency does not seem to translate into clinically adverse outcomes in ethnic minority groups to the extent that might be anticipated.

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ERRATA

Page	Original text	Type correction	Corrected text
Front page	Vitamin D deficiency and associations with gestational diabetes and neonatal body composition a multi-ethnic population.	Cor	Vitamin D deficiency and associations with gestational diabetes and neonatal body composition in a multi-ethnic population.
11 and 41	homeostatis	Cor	Homeostatic (new page 40)
17	«…in nine-year-old the children at age nine years, but …»	Cor	«… in children at the age of nine years, but…»
22	«…season when measurements 25(OH)D were performed,…»	Cor	«…season when 25(OH)D measurements were performed, …»
32	«…in Norway as at 1 January 2017…»	Cor	«…in Norway at 1 January 2017…» (new page 31)
35	Hospital	Cor	Hospitals (new page 34)
38	(see the flow chart in Figure 3.	Cor	(see the flow chart in Figure 3). (new page 37)
53 and 63	(Error! Reference source not found.)	Cor	(Figure 9). New page 52 and 62
26	Page deleted	Cpltf	
32	Space deleted	Cpltf	(Figure 1)
35	One line deleted	Cpltf	Table 2

Abbreviations for different types of corrections:

Cor = correction of language

Cpltf = change of page layout or text format

APPENDIX

Flow chart of 1918 pregnant women attending the Child Health Clinic for antenatal care in Groruddalen (May 2008 – May 2010).

The STORK Groruddalen research programme: A population-based cohort study of gestational diabetes, physical activity, and obesity in pregnancy in a multiethnic population. Rationale, methods, study population, and participation rates (reference 160).

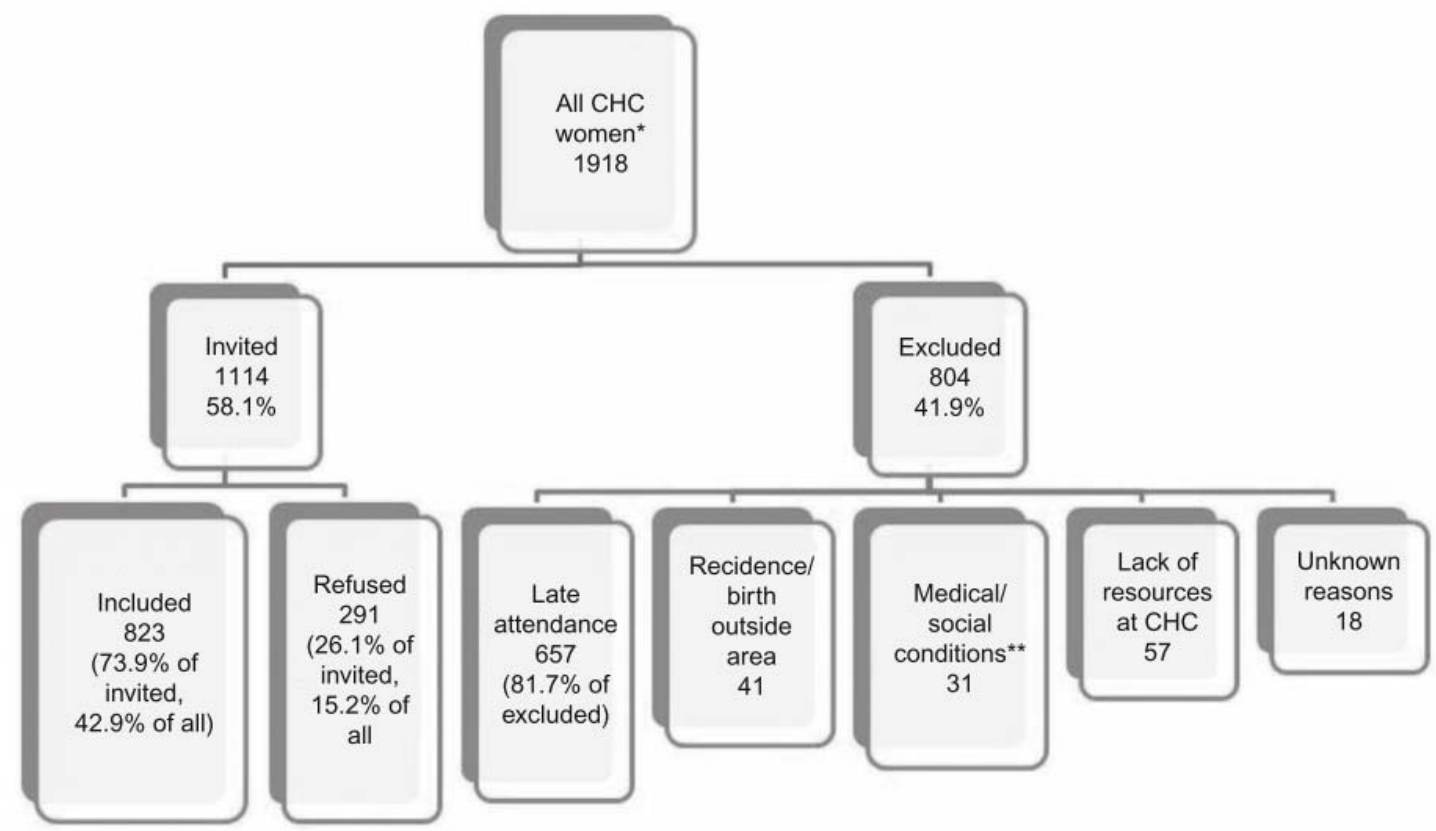
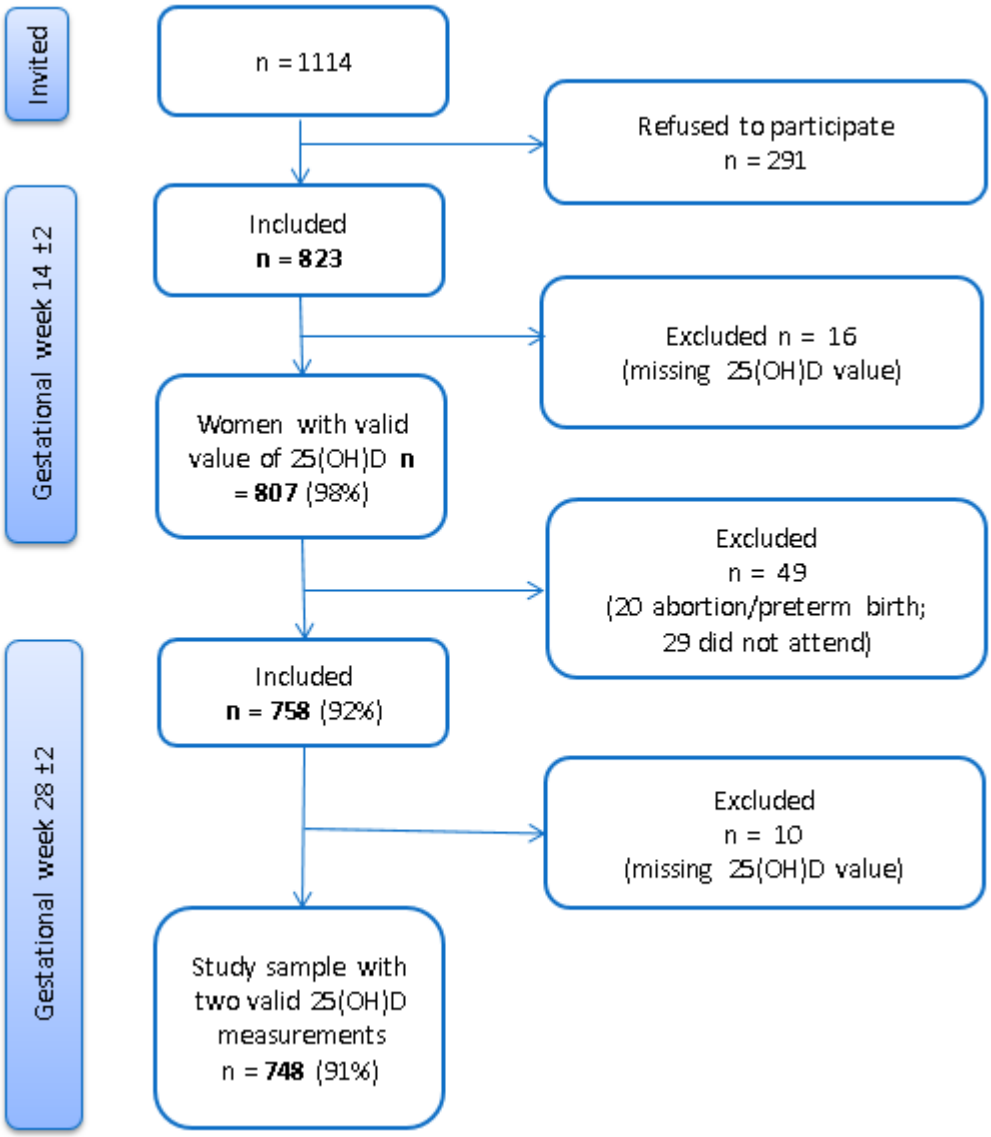
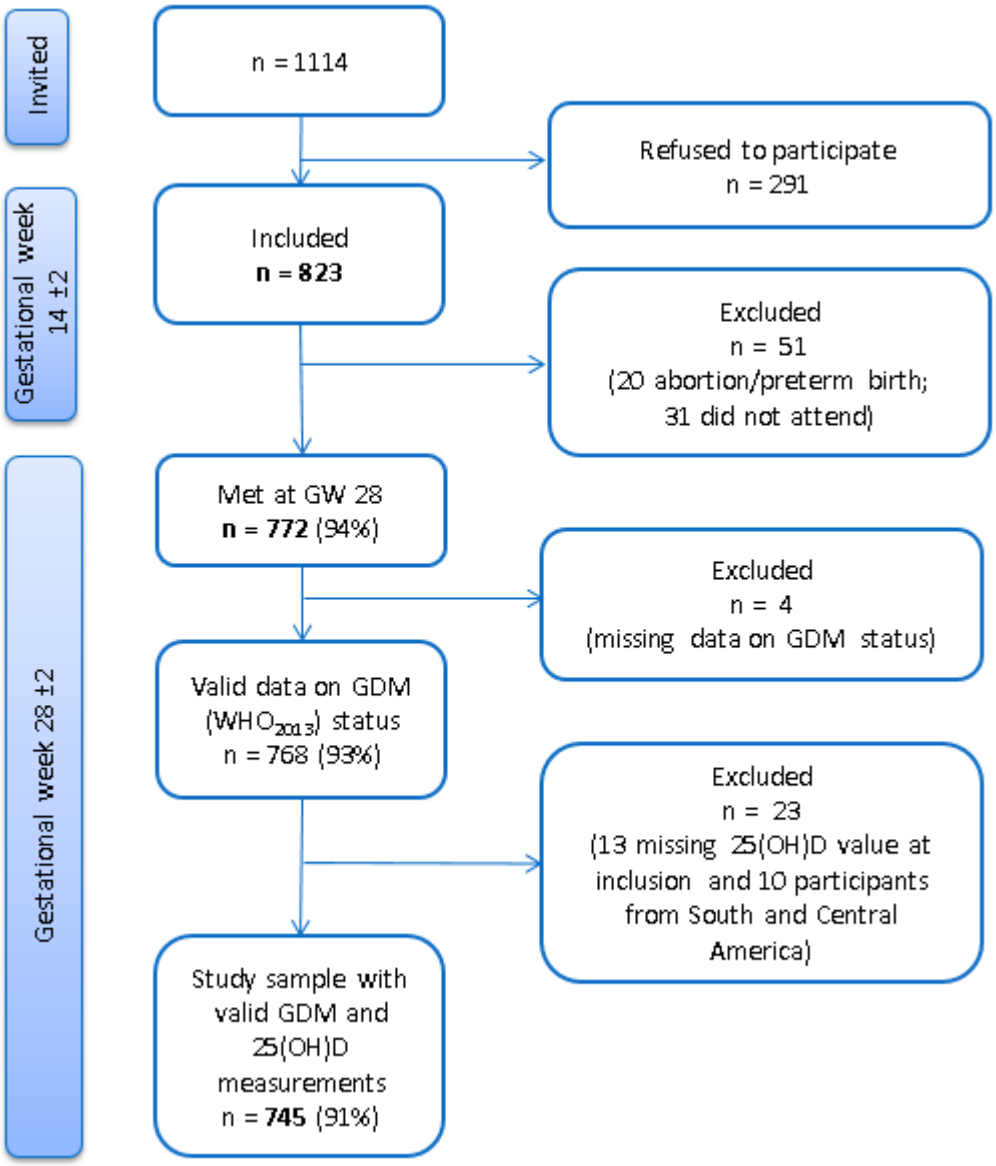


Figure 1. Attendance at the CHC from 6 May 2008 to 15 May 2010, those invited to the study, those who refused participation and those excluded categorised by reasons for not being invited. *represents number of pregnancies, of women attending the CHC in this period, 42 women represented with two pregnancies (1876 unique women). Approximately 50% of those with two pregnancies were included in their second pregnancy. **includes nine women excluded in one pregnancy as they were already included in the study.

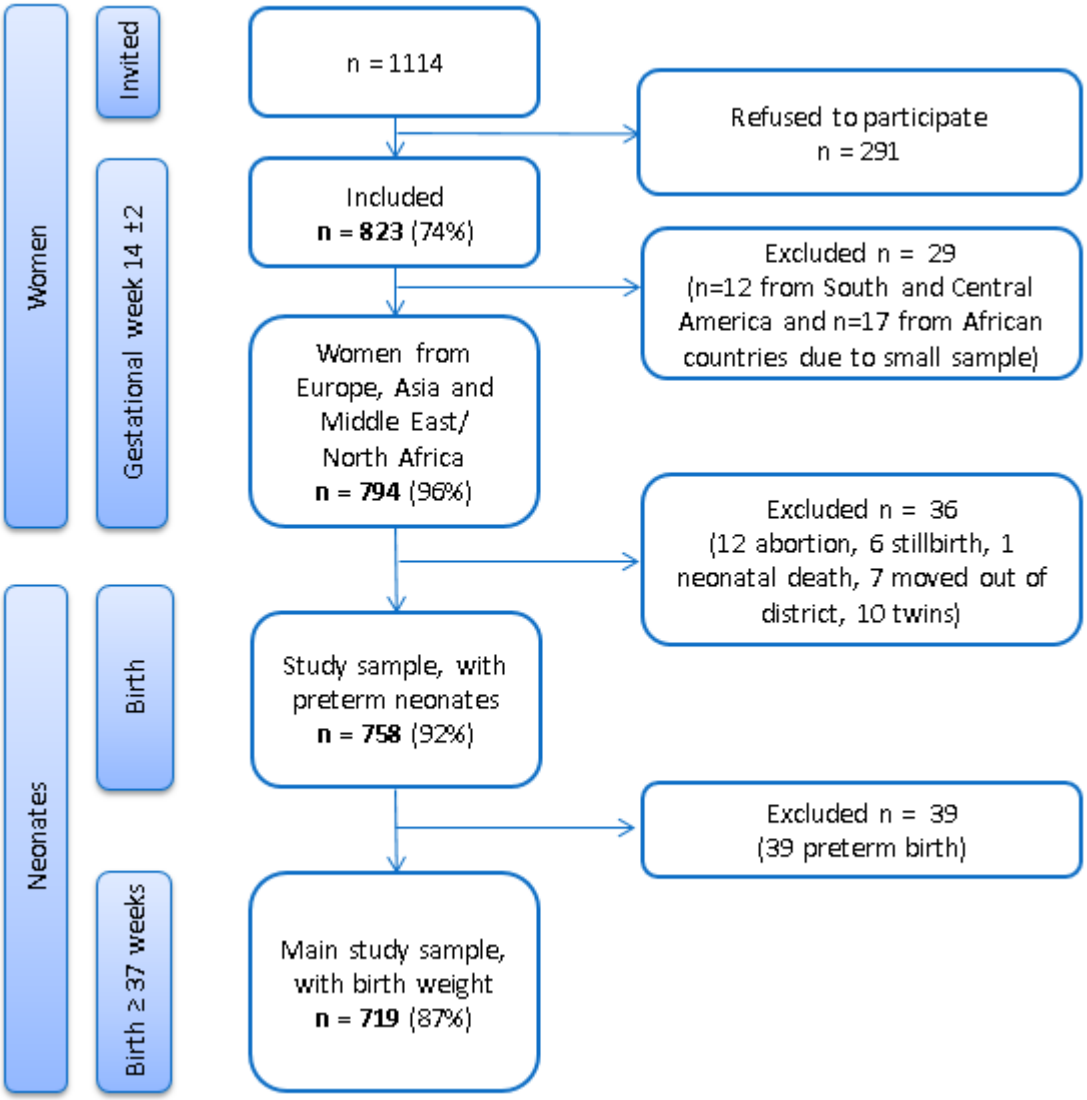
Flow chart, Paper I



Flow chart, Paper II



Flow chart, Paper III



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Unikt pas. løpenummer: ☐☐☐☐

STORK Groruddalen

CRF 1. TRIMESTER - SKJEMA 1

Kode intervjuer ☐☐

Intervjuers initialer ☐☐☐

Undersøkelsesdato ☐☐.☐☐.☐☐

Svangerskapsuke ☐☐

Kvinnens fødselsdato ☐☐.☐☐.☐☐

Bosteds-postnummer ☐☐☐☐

Undersøkelsesbydel ☐☐

Fylles ut hos alle ved første besøk på helsestasjonen i graviditeten - gjelder nesten uten unntak spørsmål som stilles for å fylle ut helsekortet - gjøres samtidig med det, unngår da å spørre om det samme to ganger. Hvis kvinnen ikke inkluderes, makuleres skjemaet. Kommentarfelt til slutt.

Forklaring til utfyllingen:
Bruk blå eller svart kulepenn. De fleste steder settes kryss eller tall. Bruk ellers store bokstaver og en bokstav per rute. Sett kryss mest mulig midt i avkryssningsboksen. Dersom feil i utfyllingen, marker dette ved å sette tre streker over boksen og kryss av på vanlig måte i den riktige boksen. Dersom behov for å notere ned ytterligere informasjon ut over hva det er avsatt plass til på skjemaet, kan du notere dette i margen. Bare sørg for at du ikke skriver i avkryssningsboksene eller notatfelter.Eksempel på utfylling:

☒ ja ☐ nei 2256 gram

Tekst i kursiv under spørsmålet, før svarkategoriene, er informasjon til intervjueren og skal ikke leses opp for kvinnen.

DEMOGRAFI

1. Hvilken sivilstand har du nå?

☐ Gift ☐ Partnerskap ☐ Samboer ☐ Enslig ☐ Skilt/separert ☐ Enke ☐ Annet

2. Hvilken utdannelse har du nå?

Kryss først av for høyeste fullførte eller avsluttede-, og evt. pågående utdanning, og angi deretter antall år for disse kategoriene. Se evt. prosedyrebok 2.4.2

			Antall år
Under 7 års skolegang	☐ Fullført	☐ Holder på med	☐☐
Grunnskole (7-9-årig skolegang)	☐ Fullført	☐ Holder på med	☐☐
1-2-årig gymnas/videreg./yrkesskole(10-11år)	☐ Fullført	☐ Holder på med	☐☐
3-årig gymnas/videreg./yrkesskole(12år)	☐ Fullført	☐ Holder på med	☐☐
Distriktshøgskole, universitet, inntil 4 år (Sykepleier, lærer, Bachelor)	☐ Fullført	☐ Holder på med	☐☐
Høgskole, universitet > 4 år (Hovedfag, Master, embetseksamen)	☐ Fullført	☐ Holder på med	☐☐

Unikt pas. løpenummer: | | | | |

3. Hva var arbeidssituasjonen for deg da du ble gravid?

- ☐ Under utdanning
- ☐ Hjemmeværende
- ☐ Arbeidssøkende/permittert
- ☐ Attføring/ufør
- ☐ Ansatt i offentlig virksomhet
- ☐ Ansatt i privat virksomhet
- ☐ Annet

Hvis annet, hva?:

4. Hva er ditt yrke? Besvares selv om du er midlertidig fraværende pga. sykdom/permisjon.
Angi yrke/stillingstittel

Angi Yrkessiffer, normalt med 4 siffer, i forhold til STRYK-klassifikasjonen. Se prosedyrebok 2.4.2, evt eget hefte. 1.siffer fremgår av nummer på hovedklassen. Hvis ikke det siste siffer er kjent, skriv de 3 første og la den siste boksen stå tom.

1.Administrative ledere og politikere				
2.Akademiske yrker				
3.Yrker med kortere høyskole og universitetsutdanning og teknikere				
4.Kontor- og serviceyrker				
5.Salgs-, service- og omsorgsyrker				
6.Yrker innen jordbruk, skogbruk og fiske				
7.Håndverkere				
8.Prosess- og maskinoperatører, transportarbeidere mv				
9.Yrker uten krav til utdanning				
0.Militære yrker og uoppgitt				
Hjemmeværende				

Hvis yrket ikke er klassifiserbart, angi:

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Unikt pas. løpenummer: ☐☐☐☐

5. Hvilket trossamfunn\religion tilhører du? *Se evt. prosedyrebok 2.4.2*

☐ Kristne kirkesamfunn *
☐ Den Ortodokse kirken
☐ Den Koptiske kirken **
☐ Den Katolske kirken
☐ Adventister
☐ Jehovas vitner
☐ Mormonere
☐ Islam
☐ Hinduisme
☐ Sikhisme
☐ Buddhisme
☐ Taoisme***
☐ Ingen trossamfunn

** fellesbetegnelse, for frimenigheter og statskirken i Norge, samt den anglikanske kirken.*
*** spesielt Etipoia, Eritrea og Egypt.*
**** Tradisjonell kinesisk religion. Spesielt kinesere og vietnamesere.*

6. Hvilket land er du født i?:

☐ Sverige
☐ Danmark
☐ Storbritannia
☐ Tyskland
☐ Tyrkia
☐ Irak
☐ Iran
☐ Pakistan
☐ Sri Lanka
☐ Vietnam
☐ Marokko
☐ Somalia
☐ Polen
☐ Russland
☐ Serbia
☐ Albania
☐ Kosovo
☐ Kina
☐ Thailand
☐ Chile
☐ Eritrea
☐ Etiopia
☐ Ghana
☐ Nigeria
☐ Annet europeisk land
☐ Annet afrikansk land
☐ Annet asiatisk land
☐ Annet amerikansk land
☐ Oceania/Australia

☐ Født i Norge av to norske foreldre
☐ Født i Norge av to utenlandske foreldre
☐ Født i Norge av en norsk + utenlandsk foreldre

7. Statsborgerskap i hvilket land?

☐ Sverige
☐ Danmark
☐ Storbritannia
☐ Tyskland
☐ Tyrkia
☐ Irak
☐ Iran
☐ Pakistan
☐ Sri Lanka
☐ Vietnam
☐ Marokko
☐ Somalia
☐ Polen
☐ Russland
☐ Serbia
☐ Albania
☐ Kosovo
☐ Kina
☐ Thailand
☐ Chile
☐ Eritrea
☐ Etiopia
☐ Ghana
☐ Nigeria
☐ Annet europeisk land
☐ Annet afrikansk land
☐ Annet asiatisk land
☐ Annet amerikansk land
☐ Oceania/Australia

Unikt pas. løpenummer: ☐☐☐☐

Hvis etnisk skandinavisk, gå til spørsmål 12.
Hvis fødeland og etnisk tilhørighet ikke synes å stemme (eks "inder", men født i Kenya, Uganda, Sør-Afrika) - besvar spørsmål 8. Ellers, gå til spørsmål 9.

8. Hvilken etnisk gruppe(felles språk, kultur, historie) føler du at du tilhører?

Angi land:

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

9. Hva er ditt morsmål?

- ☐ Urdu
- ☐ Arabisk
- ☐ Somali
- ☐ Tamilsk
- ☐ Tyrkisk
- ☐ Vietnamesisk
- ☐ Sorani
- ☐ Kinesisk
- ☐ Persisk
- ☐ Fransk
- ☐ Spansk
- ☐ Portugisisk
- ☐ Engelsk
- ☐ Tysk
- ☐ Flamsk/Nederlansk
- ☐ Annet eruopeisk språk
- ☐ Annet afrikansk språk
- ☐ Annet asiatisk språk
- ☐ Annet

10. Hvis ikke etnisk skandinavisk: Hvor gode vil du si dine norskkunnskaper er?

☐ Svært gode ☐ Gode ☐ Middels gode ☐ Litt dårlige ☐ Dårlige

11. Bruker du vanligvis tolk når du er hos lege?

☐ Ja, profesjonell ☐ Ja, familie/venn ☐ Nei

TIDLIGERE SVANGERSKAP/HELSEFORHOLD

12. Har du vært gravid tidligere? (Tenk også på svangerskap som endte med aborter eller dødfødsler)

☐ Nei ☐ Ja

Hvis nei, gå til spørsmål 14

Hvis ja:

Antall levende fødte: ☐☐ Antall dødfødte: ☐☐ Antall spontanaborter: ☐☐

Antall provoserte aborter: ☐☐ Antall svangerskap utenfor livmor: ☐☐

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Unikt pas. løpenummer: ☐☐☐☐

13. Jeg vil nå spørre deg om tidligere svangerskap som har vart mer enn 22 uker.

Hvis mer enn 1 barn per svangerskap, la tvilling 1 telle som det aktuelle nummer på barnet, tvilling 2 som neste barn.

1.barn:

Fødselsår: ☐☐☐☐ Svangerskapsuke for fødsel: ☐☐ Fødselsvekt i gram: ☐☐☐☐ Kjønn: ☐ Gutt ☐ Jente

Fødested:	Hvis flerlingefødsel:	Forløsningsmetode:	Frisk i første leveuke?:	Hvis nei:
☐ Norge	☐ Tvillinger	☐ Vanlig vaginal	☐ Ja	☐ Frisk nå
☐ Eget fødeland	☐ Trillinger	☐ Tang	☐ Nei	☐ Syk nå
☐ Annet		☐ Vakuum		☐ Død
		☐ Keisersnitt		

2.barn:

Fødselsår: ☐☐☐☐ Svangerskapsuke for fødsel: ☐☐ Fødselsvekt i gram: ☐☐☐☐ Kjønn: ☐ Gutt ☐ Jente

Fødested:	Hvis flerlingefødsel:	Forløsningsmetode:	Frisk i første leveuke?:	Hvis nei:
☐ Norge	☐ Tvillinger	☐ Vanlig vaginal	☐ Ja	☐ Frisk nå
☐ Eget fødeland	☐ Trillinger	☐ Tang	☐ Nei	☐ Syk nå
☐ Annet		☐ Vakuum		☐ Død
		☐ Keisersnitt		

3.barn:

Fødselsår: ☐☐☐☐ Svangerskapsuke for fødsel: ☐☐ Fødselsvekt i gram: ☐☐☐☐ Kjønn: ☐ Gutt ☐ Jente

Fødested:	Hvis flerlingefødsel:	Forløsningsmetode:	Frisk i første leveuke?:	Hvis nei:
☐ Norge	☐ Tvillinger	☐ Vanlig vaginal	☐ Ja	☐ Frisk nå
☐ Eget fødeland	☐ Trillinger	☐ Tang	☐ Nei	☐ Syk nå
☐ Annet		☐ Vakuum		☐ Død
		☐ Keisersnitt		

4.barn:

Fødselsår: ☐☐☐☐ Svangerskapsuke for fødsel: ☐☐ Fødselsvekt i gram: ☐☐☐☐ Kjønn: ☐ Gutt ☐ Jente

Fødested:	Hvis flerlingefødsel:	Forløsningsmetode:	Frisk i første leveuke?:	Hvis nei:
☐ Norge	☐ Tvillinger	☐ Vanlig vaginal	☐ Ja	☐ Frisk nå
☐ Eget fødeland	☐ Trillinger	☐ Tang	☐ Nei	☐ Syk nå
☐ Annet		☐ Vakuum		☐ Død
		☐ Keisersnitt		

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Unikt pas. løpenummer: ☐☐☐☐

5.barn:

Fødselsår: ☐☐☐☐

Svangerskapsuke for fødsel: ☐☐

Fødselsvekt i gram: ☐☐☐☐

Kjønn:
☐ Gutt ☐ Jente

Fødested:
☐ Norge
☐ Eget fødeland
☐ Annet

Hvis flerlingefødsel:
☐ Tvillinger
☐ Trillinger

Forløsningsmetode:
☐ Vanlig vaginal
☐ Tang
☐ Vakuum
☐ Keisersnitt

Frisk i første leveuke?:
☐ Ja
☐ Nei

Hvis nei:
☐ Frisk nå
☐ Syk nå
☐ Død

Hvis mer enn 5 barn - legg til ekstraark og stift dette sammen med resten.

14. Har du, eller har du hatt noen av følgende sykdommer? Hvis ja, angi årstall når diagnosen ble stilt.
*Sett inn årstall i boksene til høyre: *Bruk evt. kommentarfelt siste side. Se evt prosedyrebok 2.4.2*

Diabetes type 1	☐ Ja	☐ Nei	☐☐☐☐
Diabetes type 2	☐ Ja	☐ Nei	☐☐☐☐
Stoffskiftesykdom *	☐ Ja	☐ Nei	☐☐☐☐
Astma	☐ Ja	☐ Nei	☐☐☐☐
Allergi	☐ Ja	☐ Nei	☐☐☐☐
Gjentatte urinveisinfeksjoner	☐ Ja	☐ Nei	☐☐☐☐
Kronisk nyresykdom	☐ Ja	☐ Nei	☐☐☐☐
Vedvarende høyt blodtrykk	☐ Ja	☐ Nei	☐☐☐☐
Leddgikt/Bechterew	☐ Ja	☐ Nei	☐☐☐☐
Hjertesykdom *	☐ Ja	☐ Nei	☐☐☐☐
Epilepsi	☐ Ja	☐ Nei	☐☐☐☐
Underlivs-sykdom/operasjon *	☐ Ja	☐ Nei	☐☐☐☐
Ufrivillig barnløshet > 1 år	☐ Ja	☐ Nei	☐☐☐☐
Sykdom i mage/tarm	☐ Ja	☐ Nei	☐☐☐☐
Psykisk sykdom *	☐ Ja	☐ Nei	☐☐☐☐
Annet	☐ Ja	☐ Nei	☐☐☐☐

15. Hvor gammel var du da du fikk din første menstruasjon?

Angi alder i år: ☐☐

16. Har du hatt svangerskapsdiabetes i tidligere svangerskap?

Hvis ja - i hvilke(t) svangerskap? I hvilken svangerskapsuke fikk du stilt diagnosen? Brukte du insulin?

	Svangerskapsuke	Insulin
1.svangerskap	☐☐	☐ Ja ☐ Nei
2.svangerskap	☐☐	☐ Ja ☐ Nei
3.svangerskap	☐☐	☐ Ja ☐ Nei
4.svangerskap	☐☐	☐ Ja ☐ Nei
5.svangerskap	☐☐	☐ Ja ☐ Nei
6.svangerskap	☐☐	☐ Ja ☐ Nei
7.svangerskap	☐☐	☐ Ja ☐ Nei
8.svangerskap	☐☐	☐ Ja ☐ Nei

17. Er det arvelige sykdommer i familien?

☐ Ingen kjente ☐ Ja

Hvis ja, angi:

☐ Hjerte-kar sykdom ☐ Psykisk sykdom

☐ Diabetes ☐ Leddsykdom

☐ Kreftsykdom ☐ Muskelsykdom

☐ Nevrologisk sykdom ☐ Annet

Hvis annet, angi: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Hvis diabetes eller hjertesykdom, henvis til CRF 1.3 for mer detaljer

18. Er du og barnets far i slekt?

☐ Ja ☐ Nei

Hvis ja, er barnefaren din:

☐ Fetter ☐ 3-menning ☐ 4-menning ☐ Onkel ☐ Nevø ☐ Annet

19. Har du noen gang røykt/brukt snus?

Røyk:

☐ Aldri ☐ Av og til ☐ Ja, daglig

Snus:

☐ Aldri ☐ Av og til ☐ Ja, daglig

Hvis aldri på begge, gå til spørsmål 23.

20. Røykte du/brukte du snus de siste 3 månedene før du ble gravid denne gangen?

Røyk: ☐ Aldri

☐ Ja, av og til

☐ Ja, daglig

Antall sigaretter/dg ☐☐

☐☐

Snus: ☐ Aldri

☐ Ja, av og til

☐ Ja, daglig

44546

Unikt pas. løpenummer: ☐☐☐☐

21. Røyker du/snuser du nå?

Røyk: ☐ Aldri ☐ Ja, av og til ☐ Ja, daglig

Antall sigaretter/dg ☐☐ ☐☐

Snus: ☐ Aldri ☐ Ja, av og til ☐ Ja, daglig

22. Hvor gammel var du da du begynte å røyke? *Angi alder:* ☐☐

Hvis du har røykt tidligere, men ikke røyker nå, hvor gammel var du da du sluttet? *Angi alder:* ☐☐

23. Ditt alkoholforbruk:

Siste 3 mnd før svangerskap:

☐ Aldri ☐ Av og til ☐ Ja, daglig Antall alkoholenheter vanligvis: ☐☐

Nå:

☐ Aldri ☐ Av og til ☐ Ja, daglig Antall alkoholenheter vanligvis: ☐☐

Antall alkoholenheter - 1 enhet er: 1 glass vin, 0,331 øl, 1 likørglass

AKTUELT SVANGERSKAP

24. Siste menstruasjons 1.blødningsdag:

Dato: ☐☐.☐☐.☐☐☐☐

25. Termin før ultralyd:

Dato: ☐☐.☐☐.☐☐☐☐ ☐ Sikker ☐ Usikker

26. Anslå din vekt i kg:

Rett før du ble gravid: ☐☐☐ 25 år gammel: ☐☐☐ 18 år gammel: ☐☐☐

27. Anslå din høyeste og laveste vekt (i kg) utenom graviditet etter at du var 18 år.

Høyeste: ☐☐☐ Laveste: ☐☐☐

Kommentar hvis forskjell >20kg ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

EVENTUELLE VIKTIGE SUPPLERENDE KOMMENTARER TIL SVAR PÅ SPØRSMÅL:

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Du kan også gi ytterligere utfyllende kommentarer her:

TAKK FOR AT DU HAR TATT DEG TID TIL Å SVARE PÅ SPØRSMÅLENE!

[engelsk]

FORM 1.1 (CRF 1.1)

(For information: If: The interviewer must fill in the right category/code)*

1. What is your current marital status?

☐ Married ☐ Partnership ☐ Cohabitant ☐ Single ☐ Divorced/separated ☐ Widow ☐ Other

2. What is your level of education?

	Completed	Attending now	No. of years
Less than 7 years' schooling	☐	☐	☐☐
Primary school (7-9 years' schooling)	☐	☐	☐☐
1-2 years' upper sec./vocational school (10-11 yrs)	☐	☐	☐☐
3-year upper sec./vocational school (12 years)	☐	☐	☐☐
District college, university, up to 4 years (Nurse, teacher, Bachelor's degree)	☐	☐	☐☐
University college, university, more than 4 years (Master's, PhD)	☐	☐	☐☐

3. What was your work situation when you became pregnant?

☐ Attending educational institution

☐ Housewife

☐ Job-seeker/laid off

☐ Rehabilitation/disabled

☐ Employed in the public sector

☐ Employed in the private sector

☐ Other If other, what?:……

4. What is your occupation? State occupation/job title* …….
(Answer even if you are temporarily not working due to illness/leave)

5. Which religious community/religion do you belong to?* …….....

6. Which country were you born in? Indicate which country*…….....
If Norway:

☐ Born in Norway of two Norwegian parents

☐ Born in Norway of two foreign-national parents

☐ Born in Norway of one Norwegian + one foreign-national parent

7. Citizenship in which country? Indicate which country*……..

8. *(If the country of birth and ethnic group do not appear to agree (e.g. "Indian" but born in Kenya, Uganda, South-Africa)* **Which ethnic group (common language, culture, history) do you feel you belong to?: ……..**

9. What is your native language? State language* ……

10. How do you rate your Norwegian language skills?
☐ Very good ☐ Good ☐ Fair ☐ Not very good ☐ Poor

11. Do you normally use an interpreter for doctor's appointments?
☐ Yes, professional ☐ Yes, family/friend ☐ No

12. Have you been pregnant before? (Also consider pregnancies that ended in miscarriage/ abortion or with a stillbirth)
☐ No ☐ Yes If yes:
Number born alive: ☐☐ Number stillborn: ☐☐ Number of spontaneous miscarriages: ☐☐
Number of induced abortions: ☐☐ Number of ectopic pregnancies (outside the uterus): ☐☐

13. I am now going to ask you about earlier pregnancies that have lasted more than 22 weeks.
(If more than 1 child per pregnancy, count twin 1, twin 2.)

(For each child)
Year of birth: ☐☐☐☐ Pregnancy week for birth ☐☐ Baby's weight in grams ☐☐☐☐
Gender: Boy ☐ Girl ☐ Place of birth: ☐ Norway ☐ Own native country ☐ Other
Method of delivery: ☐ Normal vaginal ☐ Forceps ☐ Vacuum ☐ Caesarean section
If multiple birth: ☐ Twins ☐ Triplets
Healthy the first week?: ☐ Yes ☐ No If no: ☐ Healthy now ☐ Ill now ☐ Dead

14. Do you have/have you had any of the following illnesses?
(Some diagnoses will mean that the woman cannot take part in the study)
(If yes, state the year the diagnosis was made).

		Year
Diabetes type 1	☐ Yes ☐ No	☐☐☐☐
Diabetes type 2	☐ Yes ☐ No	☐☐☐☐
Asthma	☐ Yes ☐ No	☐☐☐☐
Allergy	☐ Yes ☐ No	☐☐☐☐
Repeated urinary tract infections	☐ Yes ☐ No	☐☐☐☐
Chronic liver disease	☐ Yes ☐ No	☐☐☐☐
Prolonged high blood pressure	☐ Yes ☐ No	☐☐☐☐

Heart disease	☐ Yes ☐ No	☐☐☐☐
Arthritis/Bechterew's disease	☐ Yes ☐ No	☐☐☐☐
Epilepsy	☐ Yes ☐ No	☐☐☐☐
Disease of the uterus/operation	☐ Yes ☐ No	☐☐☐☐
Involuntary infertility more than 1 year	☐ Yes ☐ No	☐☐☐☐
Mental illness	☐ Yes ☐ No	☐☐☐☐
Abdominal/intestinal disorder	☐ Yes ☐ No	☐☐☐☐
Metabolism disorder	☐ Yes ☐ No	☐☐☐☐
Other: ……	☐ Yes ☐ No	☐☐☐☐

15. How old were you when you menstruated for the first time? State age in years: ☐☐

16. Have you had pregnancy diabetes during a previous pregnancy?
If yes - which pregnancy? In which pregnancy week were you diagnosed? Did you use insulin?

	Pregnancy week	Insulin
1st pregnancy	☐☐	☐ Yes ☐ No
2nd pregnancy	☐☐	☐ Yes ☐ No
3rd pregnancy	☐☐	☐ Yes ☐ No
4th pregnancy	☐☐	☐ Yes ☐ No
5th pregnancy	☐☐	☐ Yes ☐ No
6th pregnancy	☐☐	☐ Yes ☐ No
7th pregnancy	☐☐	☐ Yes ☐ No
8th pregnancy	☐☐	☐ Yes ☐ No

17. Are there any inheritable diseases in the family?
☐ None I know of ☐ Yes If yes, tick the appropriate box/boxes:

☐ Cardio-vascular disease ☐ Diabetes
☐ Cancer ☐ Neurological disease
☐ Mental illness ☐ Arthritis
☐ Muscular disorder ☐ Other If other, state:……..

18. Are you and the father of the child related?
☐ Yes ☐ No

If yes, is the father of the child your:

☐ Cousin ☐ 3rd cousin ☐ 4th cousin ☐ Uncle ☐ Nephew ☐ Other

19. Have you ever smoked/used snus?

Smoked: ☐ Never ☐ Sometimes ☐ Yes, daily

Snus: ☐ Never ☐ Sometimes ☐ Yes, daily

If the answer is never to both, go to question 23.

20. Did you smoke/use snus during the last 3 months before this pregnancy?

Smoking:		Snus:
☐ Never	Number of cigarettes/daily	☐ Never
☐ Yes, sometimes	☐☐	☐ Yes, sometimes
☐ Yes, daily	☐☐	☐ Yes, daily

21. Do you smoke/use snus now?

Smoking:		Snus:
☐ Never	Number of cigarettes/daily	☐ Never
☐ Yes, sometimes	☐☐	☐ Yes, sometimes
☐ Yes, daily	☐☐	☐ Yes, daily

22. How old were you when you started to smoke? State age: ☐☐

If you have smoked previously, but do not smoke now, how old were you when you quit?

State age: ☐☐

23. Your alcohol consumption:

Last 3 months before pregnancy:

☐ Never ☐ Sometimes ☐ Yes, daily Amount of alcohol units, normally: ☐☐

Now: ☐ Never ☐ Sometimes ☐ Yes, daily Amount of alcohol units, normally ☐☐

(Number of alcohol units – 1 unit is: 1 glass of wine, 0.33 litres of beer, 1 glass of liquor)

24. Last menstruation's 1st day of bleeding:

Date:….. ….

25. Term before ultrasound:

Date:……. ☐ Certain ☐ Uncertain

26. Estimate your weight in kilos:

Right before you became pregnant: ☐☐☐ 25 years old: ☐☐☐ 18 years old: ☐☐☐

27. Estimate your highest and lowest weight (in kilos), not including pregnancies, after you turned 18 years of age.

Highest: □□□ Lowest: □□□

Comment if the difference as greater than 20 kilos ……

THANKS FOR TAKING THE TIME TO ANSWER THESE QUESTIONS!

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Unikt pas. løpenummer: ☐☐☐☐

STORK Groruddalen

CRF 1. TRIMESTER - SKJEMA 2

Kode intervjuer ☐☐ | Intervjuers initialer ☐☐☐ | Undersøkelsesdato ☐☐.☐☐.☐☐ | Svangerskapsuke ☐☐

Kvinnens fødselsdato ☐☐.☐☐.☐☐ | Bosteds-postnummer ☐☐☐☐ | Undersøkelsesbydel ☐☐

Fylles ut når kvinnen inkluderes - fortsettelsen etter spørreskjema 1 (spørsmålsnr. 1-30), sammenholdes med dette. Sp.nr. på CRF 2:31-59. Kommentarfelt til slutt.

Forklaring til utfyllingen:
Bruk blå eller svart kulepenn. De fleste steder settes kryss eller tall. Bruk ellers store bokstaver og en bokstav per rute. Sett kryss mest mulig midt i avkrysningsboksen. Dersom feil i utfyllingen, marker dette ved å sette tre streker over boksen og kryss av på vanlig måte i den riktige boksen. Dersom behov for å notere ned ytterligere informasjon ut over hva det er avsatt plass til på skjemaet, kan du notere dette i margen. Bare sørg for at du ikke skriver i avkrysningsboksene eller notatfelter.Eksempel på utfylling:

☒ ja ☐ nei 2256 gram

NB:*Tekst i kursiv under spørsmålet, før svarkategoriene, er informasjon til intervjueren og skal ikke leses opp for kvinnen.*

DEMOGRAFI

31. Hvis i lønnet arbeid - hvor stor stillingsandel hadde du de siste 3 måneder før du ble gravid? Hvor stor stillingsandel har du nå? *Gjelder uavhengig av evt. sykemelding*

Før svangerskapet ☐☐☐ % Nå ☐☐☐ %

32. Hvis i lønnet arbeid - er du fraværende fra ditt vanlige arbeid nå?

☐ Ja ☐ Nei ☐ Delvis

33. *Hvis svart ja eller delvis på spørsmål 32:* Hva er årsaken til fraværet? *Sett evt. flere kryss:*

☐ Sykemelding ☐ Permisjon ☐ Sykt barn ☐ Annet

34. Hvis i lønnet arbeid - har du vært sykemeldt i tilsammen mer enn 2 uker i løpet av dette svangerskapet? *Se evt. prosedyrebok 2.4.2*

Helt sykemeldt: Hvis ja, angi ca antall uker: ☐☐

Delvis sykemeldt: Hvis ja, angi ca antall uker: ☐☐

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Unikt pas. løpenummer: ☐☐☐☐

36. Tenk på deg selv som 10-åring. Hvilket yrke hadde mor/far da du vokste opp.

Angi Yrkessiffer, normalt med 4 siffer, i forhold til STRYK-klassifikasjonen. Se eget hefte. 1.siffer fremgår av nummer på hovedklassen. Hvis ikke det siste siffer er kjent, skriv de 3 første og la den siste boksen stå tom. Se evt. prosedyrebok 2.4.2

	MOR	FAR
1.Administrative ledere og politikere	☐☐☐☐	☐☐☐☐
2.Akademiske yrker	☐☐☐☐	☐☐☐☐
3.Yrker med kortere høyskole og universitetsutdanning og teknikere	☐☐☐☐	☐☐☐☐
4.Kontor- og serviceyrker	☐☐☐☐	☐☐☐☐
5.Salgs-, service- og omsorgsyrker	☐☐☐☐	☐☐☐☐
6.Yrker innen jordbruk, skogbruk og fiske	☐☐☐☐	☐☐☐☐
7.Håndverkere	☐☐☐☐	☐☐☐☐
8.Prosess- og maskinoperatører, transportarbeidere mv	☐☐☐☐	☐☐☐☐
9.Yrker uten krav til utdanning	☐☐☐☐	☐☐☐☐
0.Militære yrker og uoppgitt	☐☐☐☐	☐☐☐☐
Hjemmeværende	☐☐☐☐	☐☐☐☐

Hvis yrket ikke er klassifiserbart, angi (MOR): ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Hvis yrket ikke er klassifiserbart, angi (FAR): ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

37. Tenk på deg selv som 10 åring. Hvor mange oppholdsrom var det i leiligheten/boligen deres?
Ikke regn med kjøkken og evt bad. Angi antall rom ☐☐

Hvor mange personer bodde i leiligheten/boligen?
Angi antall personer ☐☐

Eide din mor/far evt. dine foresatte bil? ☐ Ja ☐ Nei

38. Hva var din mors alder da du ble født? ☐☐

39. Hvor mange søsken har du? (*Med samme mor*) ☐☐ Evt. halvsøsken? *Angi antall evt.* ☐☐

40. Hvilket nummer i søskenflokken var du?
(Med samme mor) ☐☐

41. Hvor lenge har du samlet bodd i: *(Angi antall år)*

Den bydelen du nå bor i: ☐☐ Oslo: ☐☐

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Unikt pas. løpenummer: ☐☐☐☐

42. Hvor bodde du det meste av tiden før du fylte 16 år?
*Se evt liste over bydeler i områder i Oslo i prosedyrebok 2.4.2. Ved * eller ** gå til aktuell merknad*

☐ I samme bydel som nå ☐ I annen bydel/område i Oslo* ☐ I annet fylke i Norge ☐ Utenfor Norge **

Angi evt. tidligere bydel:

☐ Indre Øst (Gamle Oslo,Sagene, Torshov, Grunerløkka-Sofienberg)

☐ Indre Vest (Frogner, Majorstua-Uranienborg, St.Haugen)

☐ Ytre Øst (Groruddalen,Helsfyr, Østensjø,Lambertseter, Bøler, Søndre Nordstrand)

☐ Ytre Vest (Ullern, Røa, Vinderen, Sogn, Grefsen-Kjelsås,Nordstrand,Ekeberg-Bekkelaget)

**Hvis utenfor Norge:*

☐ I eget fødeland ☐ Annet

43. Hvem deler du husholdning med? *Sett evt. flere kryss*

☐ Ektefelle/samboer ☐ Foreldre ☐ Svigerforeldre ☐ Barn ☐ Ingen ☐ Andre, beskriv:

☐☐☐☐☐☐☐☐☐☐

44. Hvor mange personer er det i husholdningen? Tell med deg selv

Antall personer 18 år eller over ☐☐ Antall personer 12-17år ☐☐

Antall personer 6-11år ☐☐ Antall personer under 6 år ☐☐

45.Hvor mange oppholdsrom (ikke regn med kjøkken og evt bad) er det i leiligheten/boligen der du bor? *Angi antall rom* ☐☐

Boligtype:

☐ Leilighet i blokk/hus med flere boenheter, som 4mannsbolig ☐ Rekkehus ☐ Enebolig ☐ Annet

Eier eller leier du/dere boligen? ☐ Eier ☐ Leier

Hvis født i Norge av to norske foreldre, gå til sp. 52

46. Hvis 1.generasjons innvandrer: Hvor lenge har du bodd i Norge?
Angi antall år ☐☐

Hvis mor ikke er 1. eller 2. generasjons innvandrere, gå til sp. 52

47. Er du etterkommer etter innvandrerforeldre/foreldre som ikke er født i Norge?

☐ Ja ☐ Nei

Hvis ja:

☐ Født i Norge, men begge foreldre født i utlandet

☐ Utenlandsfødt med en norskfødt forelder

☐ Norskfødt med en utenlandskfødt forelder

☐ Utenlandskfødt med utenlandske foreldre

☐ Utenlandsadoptert

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Unikt pas. løpenummer: ☐☐☐☐

Hvis du er født i Norge, men begge foreldre er født i utlandet, angi fødeland for dine foreldre:

Fødeland for din mor:			Fødeland for din far:		
☐ Norge	☐ Vietnam	☐ Chile	☐ Norge	☐ Vietnam	☐ Chile
☐ Sverige	☐ Marokko	☐ Eritrea	☐ Sverige	☐ Marokko	☐ Eritrea
☐ Danmark	☐ Somalia	☐ Etiopia	☐ Danmark	☐ Somalia	☐ Etiopia
☐ Storbritannia	☐ Polen	☐ Ghana	☐ Storbritannia	☐ Polen	☐ Ghana
☐ Tyskland	☐ Russland	☐ Nigeria	☐ Tyskland	☐ Russland	☐ Nigeria
☐ Tyrkia	☐ Serbia	☐ Annet eur. land	☐ Tyrkia	☐ Serbia	☐ Annet eur. land
☐ Irak	☐ Albania	☐ Annet afrik. land	☐ Irak	☐ Albania	☐ Annet afrik. land
☐ Iran	☐ Kosovo	☐ Annet asia. land	☐ Iran	☐ Kosovo	☐ Annet asia. land
☐ Pakistan	☐ Kina	☐ Annet amer.land	☐ Pakistan	☐ Kina	☐ Annet amer.land
☐ Sri Lanka	☐ Thailand	☐ Oceania/Australia	☐ Sri Lanka	☐ Thailand	☐ Oceania/Australia

Sp 48 gjelder hvis mor er 1. og 2. generasjons innvandrer (person som selv er født utenfor Norge eller med en eller begge foreldrene født utenfor Norge). Gjelder ikke hvis adoptert.

48. Hvis ikke født i Norge og ikke norske foreldre, på hvilket grunnlag kom du til Norge?

☐ Arbeid
☐ Ekteskap med norsk
☐ Familiegjenforening
☐ Flyktning
☐ Opphold på humanitært grunnlag
☐ Annet ☐☐☐☐☐☐☐☐☐☐

49. *Hvis 1. eller 2. generasjons innvandrer (uten norske foreldre)* Hvor ofte har du i løpet av det siste året:

Lest avis på eget språk/foreldres morsmål	☐ Daglig	☐ Ukentlig	☐ Sjeldere	☐ Aldri
Lest norsk avis/sett på norsk TV	☐ Daglig	☐ Ukentlig	☐ Sjeldere	☐ Aldri
Hatt besøk av minst en nordmann	☐ Daglig	☐ Ukentlig	☐ Sjeldere	☐ Aldri
Fått hjelp/støtte av minst en nordmann	☐ Daglig	☐ Ukentlig	☐ Sjeldere	☐ Aldri
Deltatt i møter arrangert av egne/foreldres landsmenn	☐ Daglig	☐ Ukentlig	☐ Sjeldere	☐ Aldri

50. Har du her i landet opplevd å bli nektet å leie eller kjøpe bolig på grunn av din innvandrerbakgrunn?

☐ Ja, helt sikkert ☐ Ja, jeg har mistanke om det ☐ Nei ☐ Vet ikke

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Unikt pas. løpenummer: ☐☐☐☐

51. Har du her i landet i løpet av de siste 5 årene opplevd å få nei til en jobb du søkte på grunn av din innvandrerbakgrunn?

☐ Ja, helt sikkert ☐ Ja, jeg har mistanke om det ☐ Nei ☐ Vet ikke

AKTUELLE SVANGERSKAP

52. Hvordan var helsen din de siste 3 måneder før svangerskapet?

☐ Dårlig ☐ Ikke helt god ☐ God ☐ Svært god

53. Var dette svangerskapet planlagt?

☐ Ja ☐ Nei ☐ Delvis Evt. kommentar: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

54. Hvis planlagt, hvor lenge har du prøvd å bli gravid? *Angi antall måneder*

☐☐☐

55. Har du i dette svangerskapet smerter i noen av de følgende kroppsdeler?
Intervjuer ber kvinnen peke på aktuelt sted på egen kropp og plansje, se prosedyrebok 2.4.2. Sett kryss for aktuell lokalisasjon. Du kan sette flere kryss.

I korsryggen uten utstråling til bein(a)	☐ Nei	☐ En del plaget	☐ Sterkt plaget
I korsryggen med utstråling til bein(a)	☐ Nei	☐ En del plaget	☐ Sterkt plaget
Foran i bekkenet, over kjønnsbeinet(symfysen)	☐ Nei	☐ En del plaget	☐ Sterkt plaget
Bak, over det ene bekkenleddet	☐ Nei	☐ En del plaget	☐ Sterkt plaget
Bak, over begge bekkenleddene	☐ Nei	☐ En del plaget	☐ Sterkt plaget
Foran og bak på ene siden av bekkenet	☐ Nei	☐ En del plaget	☐ Sterkt plaget
Foran og bak på begge sider av bekkenet	☐ Nei	☐ En del plaget	☐ Sterkt plaget

56. Tenk tilbake på de siste 14 dager. Har du tatt/brukt tran/trankapsler og/eller andre kosttilskudd i løpet av disse dagene? *Hvis ja, angi antall kapsler/tabletter/skjeer per dag på rett frekvens*

	Aldri	<1g/uke	1-2g/uke	3-4g/uke	5-6x/uke	Daglig
Tran/Trankapsler	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Fiskeoljekapsler	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Seloljekapsler	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Folat	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Jerntilskudd* *Angi evt. navn på neste side*	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Multivitaminer uten mineraler (som Sanasol,BioVit,Vitaplex oa)	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Multivitaminer m/mineraler (som Vitamineral,Kostpluss, Solaray Spektro oa)	☐	☐☐	☐☐	☐☐	☐☐	☐☐
Andre kosttilskudd *Angi evt. navn på neste side*	☐	☐☐	☐☐	☐☐	☐☐	☐☐

Angi evt. andre kosttilskudd her:

Angi navn på kosttilskudd 1:

Angi navn på kosttilskudd 2:

Angi navn på kosttilskudd 3:

Angi navn på kosttilskudd 4:

**Navn på jerntilskudd:*

57. Har du brukt faste medisiner, inkludert prevensjon, de siste 3 måneder før svangerskapet?
Angi legemiddel navn - og evt. sykdom/plage

Angi legemiddelnavn — Evt sykdom/plage

Angi legemiddelnavn — Evt sykdom/ plage

Angi legemiddelnavn — *Evt sykdom/ plage*

Angi legemiddelnavn — *Evt sykdom/ plage*

Angi legemiddelnavn — *Evt sykdom/ plage*

☐ **P-piller** ☐ **Minipiller** ☐ **Spiral**

Merke

58. Har du brukt faste medisiner i dette svangerskapet? *Angi legemiddel navn - for sykdom/plage*

Angi legemiddelnavn — Evt sykdom/plage

Angi legemiddelnavn — Evt sykdom/ plage

Angi legemiddelnavn — *Evt sykdom/ plage*

Angi legemiddelnavn — *Evt sykdom/ plage*

Angi legemiddelnavn — *Evt sykdom/ plage*

8852

Unikt pas. løpenummer: ☐☐☐☐

59. Har du opplevd noen av de følgende livshendelser eller problemer i løpet av de siste 6 måneder?

Du har selv vært utsatt for alvorlig sykdom, skade eller overfall	☐ Ja	☐ Nei
En i din nærmeste familie (mor eller far, ektefelle/samboer, barn eller søsken) har vært alvorlig syk, utsatt for skade eller overfall	☐ Ja	☐ Nei
En i din nærmeste familie (mor eller far, ektefelle/samboer, barn eller søsken) er avgått ved døden	☐ Ja	☐ Nei
Du er separert/skilt, eller har brutt et langvarig forhold	☐ Ja	☐ Nei
Du har hatt problemer/store bekymringer med barna dine (oppdragelse, skole, disiplin)	☐ Ja	☐ Nei
Du har blitt arbeidsledig, eller søkt forgjeves etter jobb i mer enn 1 måned	☐ Ja	☐ Nei
Du har opplevd andre belastende forhold, som et alvorlig problem med en nær venn, nabo, slektning eller partner, alvorlige økonomiske bekymringer, noe du satte stor pris på ble mistet eller stjålet, dødsfall hos annen nærstående, eller opplever store problemer på jobb	☐ Ja	☐ Nei

EVENTUELLE VIKTIGE SUPPLERENDE KOMMENTARER TIL SVAR PÅ SPØRSMÅL:

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Spørsmålsnummer: ☐☐ Kommentar ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

TAKK FOR AT DU HAR TATT DEG TID TIL Å SVARE PÅ SPØRSMÅLENE!

[engelsk]

Case Record FORM 1.2

31. If you are in paid employment – how large a percentage of fulltime employment did you have during the last three months before you became pregnant? What percentage do you have now?
(Applies regardless of any sick leave)

Before pregnancy: □□□ % Now: □□□ %

32. If you are in paid employment – are you currently absent from your normal job?

□ Yes □ No □ Partly

33. (If your answer to question 32 was "Yes" or "Partly") **What is the reason for your absence?**

□ Sick leave □ Leave □ Sick child □ Other

34. If you are in paid employment – have you been on sick leave for more than two weeks during this pregnancy?

Full sick leave: Partial sick leave:

If yes, state the approx. number of weeks: □□ If yes, state the approx. number of weeks: □□

36. Think back to when you were 10 years old. What occupation did your mother/father have?

MOTHER…… FATHER……..

37. Think back to when you were 10 years old. How many rooms did your flat/dwelling have?

(Don't count kitchen and bathroom). State number of rooms: □□

How many people lived in the flat/dwelling? State number of people: □□

Did your mother/father/guardian own a car? □ Yes □ No

38. How old was your mother when you were born? □□ years of age

39. How many brothers and sisters (siblings) do you have? □□ (With the same mother)

40. Which number were you among your siblings? □□ (With the same mother)

Any half-siblings? State number, if any □□

41. How long have you lived in: (State the number of years)

The city district you currently live in: □□ Oslo: □□

42. Where did you live for most of the time before you turned 16 years of age?

□ In the same city district as now □ In another city district/area of Oslo □ In another county in Norway
□ Outside Norway

State any previous city districts:……..

If outside Norway: ☐ In own country of origin ☐ Other

43. Who do you share your household with?

☐ Spouse/cohabitant ☐ Parents ☐ Parents-in-law ☐ Child/children ☐ No one

☐ Other(s), describe:…….

44. How many persons are there in your household? Count yourself as well

Number of persons 18 or older: ☐☐ Number of persons 12-17 years of age: ☐☐

Number of persons 6-11 years of age: ☐☐ Number of persons under 6 years of age: ☐☐

45. How many rooms are there (don't count kitchen and bathroom) in the flat/dwelling where you live? State number of rooms: ☐☐

Type of dwelling:

☐ Flat in a block of flats/house with several housing units, e.g. quadruplex (four units)

☐ Terrace/row house

☐ Detached house ☐ Other

Do you own or rent your dwelling? ☐ Own ☐ Rent

46. If you are a first generation immigrant: How long have you lived in Norway?

State number of years: ☐☐

47. Are you the descendant of immigrant parents/parents who were not born in Norway?

☐ Yes ☐ No

If yes:

☐ Born in Norway, but both parents born abroad

☐ Born abroad with one parent born in Norway

☐ Born in Norway with one parent born abroad

☐ Born abroad of foreign-national parents

If you were born in Norway, with both parents born abroad, state the country of origin of your parents:
Country of origin for: your mother:…… your father:……

48. On what grounds did you come to Norway?

☐ Work

☐ Married a Norwegian

☐ Family reunification

☐ Refugee

☐ Residence on humanitarian grounds

☐ Other

49. How often in the course of the last year have you:

Read a newspaper in your own language/parents' native language:	☐ Daily	☐ Weekly	☐ Less than weekly	☐ Never
Been visited by at least one Norwegian:				
Read a Norwegian newspaper/watched Norwegian TV:				
Received help/support from at least one Norwegian:				
Participated in a meeting arranged by your own/parents' countrymen:				

50. Have you here in Norway experienced being denied a chance to rent or buy a dwelling because of your immigrant background?

☐ Yes, definitely ☐ Yes, I suspect so ☐ No ☐ Don't know

51. During the last five years in Norway have you experienced being denied a job you applied for due to your immigrant background?

☐ Yes, definitely ☐ Yes, I suspect so ☐ No ☐ Don't know

52. What was your state of health the last three months before your pregnancy?

☐ Poor ☐ Not too good ☐ Good ☐ Very good

53. Was this pregnancy planned?

☐ Yes ☐ No ☐ Partially Any comments:…….

54. If planned, how long have you been trying to get pregnant? State number of months: ☐☐

55. Have you had any pain in any of the following parts of your body during your pregnancy?

In the lower back <u>not</u> radiating to the leg(s)	☐ No pain	☐ Some pain	☐ Much pain
In the lower back <u>with</u> it radiating to the leg(s)	☐	☐	☐
In the front of the pelvic bone, over the pubic bone (symphysis)	☐	☐	☐
Back, over <u>one</u> pelvic joint	☐	☐	☐
Back, over <u>both</u> pelvic joints	☐	☐	☐
Front and back of <u>one side</u> of the pelvic bone	☐	☐	☐
Front and back of <u>both sides of the</u> pelvic bone	☐	☐	☐

56. Think back over the last 14 days. Have you taken cod-liver oil/cod-liver oil capsules/pills (*tran*) and/or other dietary supplements during this time? If yes, state the number of capsules/pills/spoons per day and the correct frequency.

Cod-liver oil/Cod-liver oil capsules: ☐ Never ☐ <Once a week ☐ 1-2 times a week ☐ 3-4 times a week ☐ 5-6 times a week ☐ Every day
Fish oil capsules:
Seal oil capsules:
Folate (vitamin B):
Iron supplement:
Multi-vitamins with minerals (e.g. *Vitamineral, Kostpluss, Solaray Spektro* etc.):
Multi-vitamins without minerals: (e.g. *Sanasol, BioVit, Vitaplex* etc.)
Other dietary supplement:

State the name of the dietary supplement:…….
State the name of any iron supplements:…….

57. Have you taken medication regularly, including birth-control, the last three months before your pregnancy?
State the name of the medication……. – and the illness/disorder, if any……..

☐ The pill ☐ Mini-pill ☐ IUD/coil Brand/name:…….

58. Have you taken medication regularly during this pregnancy?
State the name of the medication……. – and the illness/disorder, if any……..

59. Have you experienced any of the following events or problems in your life during the last six months?

You have been stricken with a serious illness, been injured or assaulted ☐ Yes ☐ No

One of your closest family members (mother or father, spouse/cohabitant, children or brothers/sisters) has been seriously ill, injured or the victim of an assault ☐ Yes ☐ No

One of your closest family members (mother or father, spouse/cohabitant, children or brothers/sisters) has died ☐ Yes ☐ No

You have separated/divorced, or have broken off a long-term relationship ☐ Yes ☐ No

You have had problems/major concerns about your children (upbringing, school, discipline) ☐ Yes ☐ No

You have become unemployed or been searching in vain for a job for more than one month ☐ Yes ☐ No

You have experienced other difficult circumstances, e.g. a serious problem with a close friend, neighbour, relative or partner, serious financial concerns, something you valued dearly has been lost or stolen, death of someone close to you, or have major problems at work

☐ Yes ☐ No

ANY IMPORTANT SUPPLEMENTAL COMMENTS ON YOUR ANSWERS TO THE QUESTIONS:

Question number: ☐☐ Comment……

You can also add more detailed comments here: ……

THANKS FOR TAKING THE TIME TO ANSWER THESE QUESTIONS!

47111

Unikt pas. løpenummer: ☐☐☐☐

STORK - Antropometri barn

Kode intervjuer ☐☐ Intervjuers initialer ☐☐☐ Undersøkelsesdato ☐☐.☐☐.☐☐ Kl. ☐☐,☐☐ Sykehus ☐

Kvinnens fødselsdato ☐☐.☐☐.☐☐ Barnets fødselsdato ☐☐.☐☐.☐☐ Kl. ☐☐,☐☐

	1. måling:	2. måling:
Vekt ved fødsel (g)	☐☐☐☐	☐☐☐☐
Vekt ved dagens mål (g)	☐☐☐☐	
Lengde (cm)	☐☐,☐	☐☐,☐
CRL (cm)	☐☐,☐	☐☐,☐
HO (cm)	☐☐,☐	☐☐,☐
Omkrets abdomen v/navle (cm):	☐☐,☐	☐☐,☐
Omkrets abd. v/sternum (cm)	☐☐,☐	☐☐,☐
Omkrets lår (cm)	☐☐,☐	☐☐,☐
Omkrets overarm (cm)	☐☐,☐	☐☐,☐
Caliper overarm (mm)	☐☐,☐	☐☐,☐
Caliper fremside lår (mm)	☐☐,☐	☐☐,☐
Caliper midje (mm)	☐☐,☐	☐☐,☐
Caliper subscapula (mm)	☐☐,☐	☐☐,☐

STORK
Groruddalen

Oslo ……..

TIL DEG SOM DELTAR I STORK - PROSJEKTET

I blodprøvene som ble tatt av deg nylig, viste det seg at du har for lite vitamin D. Dette er ikke farlig, verken for deg eller barnet ditt, men betyr at du bør ta tilskudd av dette vitaminet.

Verdien for 25-OH-Vitamin D, tatt …….. og analysert på Hormonlaboratoriet, Aker universitetssykehus var:…….nmol/l.

Vi råder deg til å ta kontakt med fastlegen din, fordi du trenger vitamin D på resept. For å gjøre arbeidet lettere for han/ henne har vi laget et skriv med behandlingsråd, som du finner vedlagt. Ta med hele dette brevet til legen din.

Når du er ferdig med behandling bør du gå over til å ta vanlig vitamin D tilskudd, for eksempel i form av to trankapsler eller en spiseskje tran daglig (fåes på apotek eller dagligvarebutikk).

På baksiden av brevet kan du lese mer om vitamin D.
Dersom du har ytterligere spørsmål omkring dette kan du kontakte en av legene i prosjektet på telefon: 23 03 34 29.

Med vennlig hilsen

…….
Jordmor i STORK prosjektet

STORK
Groruddalen

INFORMASJON OM VITAMIN D

Vitamin D er et viktig vitamin, som bidrar bl.a. til et sterkt skjelett. Hos barn betyr det at knoklene vokser riktig og blir rette og sterke, og hos voksne at man unngår beinskjørhet og brudd.
Man tror også at vitamin D kan motvirke flere sykdommer som en del kreftformer, infeksjoner og sykdommer i immunforsvaret.

Hvordan får man nok vitamin D?

Man får vitamin D ved å sole seg og spise mat som er rik på dette vitaminet, som fet fisk (makrell, laks, ørret, sild), "ekstra lett" melk som er tilsatt vitamin D, eller ved å ta tran eller trankapsler.
Om vinteren er mat med mye D-vitamin eller ekstra tilskudd ekstra viktig.

Hvem er utsatt for vitamin D mangel?

For gravide, spedbarn og eldre er vitamin D ekstra viktig. Kvinner som dekker til store deler av kroppen, spesielt når de er bosatt i nordiske land, kan være særlig utsatt for mangel. I tillegg finnes enkelte sjeldne sykdommer.
Mangel på vitamin D gir ikke alltid tydelige symptomer, men kan hos voksne gi tretthet, uopplagthet og diffuse smerter i musklene, nederst i ryggen og i beina.
Mangel på vitamin D kan oppdages i blodprøver.

Hvordan behandles mangel på vitamin D?

Mange i Norge har for lite vitamin D i kroppen. De fleste vil derfor ha nytte av tilskudd med vitamin D. Det får man lettest ved å ta tran eller trankapsler eller kosttilskudd som inneholder vitamin D.
Alle gravide anbefales å ta vitamin D tilskudd.

Man bør ikke få for mye vitamin D. Ta derfor aldri mer enn pakningen sier uten å ha avtalt dette med legen din.

Ved mer alvorlig D-vitaminmangel må man i enkelte tilfeller bruke sterkere medisiner som fås på resept hos lege.

BEHANDLING AV VITAMIN D MANGEL HOS GRAVIDE

Moderat mangel: 25-OH Vitamin D 12-37 nmol/l

Anbefalt behandling: (reseptpliktige legemidler)

2 tyggetabletter "Weifa-kalsium med D-vitamin 500/400IE" daglig
(tilsvarer 800IE (20µgr) vitamin D3 og 1000mg kalk)

eller:

2 tyggetabletter "Calcigran Forte" daglig
(innholder det samme som ovenstående alternativ).

Alternativ behandling: (reseptfrie legemidler)

2 Nycoplus D-vitamin svelgetabletter á 10 µgr daglig (tilsvarer 20 µgr vitamin D3)
+ 2 Weifa Calsium tyggetabletter á 500mg daglig.

Videre oppfølging:

- Behandles i 1 - 3 mnd.
- Deretter kontroll med blodprøver (25-OH-Vitamin D, evt. også PTH, i-Ca).
- Dersom tilfredsstillende verdier (dvs helst over 50 nmol/l), gå over til:

Forebyggende behandling: 5 ml tran eller 2 trankapsler daglig.

Betydelig mangel: 25-OH Vitamin D <12 nmol/l

Anbefalt behandling:

Som for moderat mangel + 1 Nycoplus D-vitamin svelgetablett á 10 µgr.
(tilsvarer 30 µgr vitamin D3 og 1g kalk).

Alternativ behandling:

3 Nycoplus D-vitamin svelgetabletter á 10 µgr.
(tilsvarer 30 µgr vitamin D3).
+ 2 Weifa Calsium tyggetbl á 500mg.

Videre oppfølging:

- Behandles i 3 mnd.
- Deretter kontroll med blodprøver: (25-OH-Vitamin D og PTH, i-Ca).
- Dersom tilfredsstillende verdier (dvs helst over 50 nmol/l), gå over til:

Forebyggende behandling: 5 ml tran eller 2 trankapsler daglig.

NB: Det er uheldig å øke antall trankapsler eller tranmengde ut over dette da det gir høy dose av andre vitaminer, f.eks. vitamin A ,som er toksisk i for høye doser.

Versjon 4.11.08

Aker universitetssykehus HF

Til deg som er gravid og bor i bydelene Stovner, Grorud og Bjerke

Forespørsel om å delta i forskningsprosjektet "STORK Groruddalen"

Hensikten med studien

Formålet er å videreutvikle svangerskaps- og fødselsomsorgen og helsestasjonstjenesten slik at vi bedre kan forebygge og behandle nye helseproblemer som overvekt, inaktivitet og diabetes. Kvinner med diabetes og deres barn har noe høyere risiko for komplikasjoner i svangerskapet. Noen ganger oppstår diabetes i svangerskapet. Selv om tilstanden vanligvis går over etter fødselen, er det økt risiko for å få type 2 diabetes senere.

Vi som arbeider på helsestasjonene i bydelene Stovner, Grorud og Bjerke, ønsker i samarbeid med universitetssykehusene i Osloområdet å kartlegge disse problemene, hvordan de påvirker helsetilstanden for mor og barn på kort og lang sikt, og finne årsakene til at svangerskapsdiabetes og type 2 diabetes øker. Aker universitetssykehus er ansvarlig for studien.

Hva innebærer studien?

Du vil på helsestasjonen få en ekstra og en utvidet kontroll i svangerskapet og en ekstra undersøkelse etter fødselen. Vi vil ta noen ekstra blod- og urinprøver og målinger, og be deg svare på spørsmål om din helse, fysiske aktivitet og kosthold. Du vil også få ekstra ultralyd-undersøkelser i svangerskapet. Det tas noen blodprøver fra barnets navlesnor og morkaken ved fødselen, og noen undersøkelser og blodprøver av barnet senere.

Hva skjer med prøvene og informasjonen om deg?

Dette skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kodeliste som knytter sammen studieresultatene og deltakernes navn, er kun tilgjengelig for autorisert helsepersonell knyttet til studien, og denne vil bli slettet ved studieslutt, senest i 2030. Det vil selvsagt ikke være mulig å identifisere deltakerne når resultatene av studien offentliggjøres. For å finne ut hvor mange som får diabetes og/eller hjerte- og karsykdom i fremtiden, ønsker vi å kunne hente ut disse opplysningene fra din fastlege og fra sykehus der du får behandling, og fra Norsk Diabetesregister for voksne, Norsk Pasientregister, Reseptregistret, Dødsårsaksregistertet og Medisinsk fødselsregister.

Frivillig deltakelse

Det er frivillig å delta i studien, og alle har rett til betenkningstid før man bestemmer seg. De som ikke ønsker å delta, trenger ikke å oppgi grunn, og det får ingen konsekvenser for den videre behandlingen. Hvis du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan senere trekke tilbake samtykket uten at det påvirker behandlingen, ved å kontakte prosjektleder dr. med. Anne Karen Jenum (telefon 91 18 14 16).

Mer informasjon om studien finnes i *Kapittel A*
Mer informasjon om biobank, personvern økonomi og forsikring finnes i *Kapittel B*

Kapittel A- utdypende forklaring om hva studien innebærer

Alle gravide som går til svangerskapskontroll i bydelene Stovner, Grorud og Bjerke, vil bli invitert til å delta i studien. Hvis du sier ja til å delta, vil vi be deg møte til en ekstra undersøkelse på helsestasjonen omkring uke 12, en utvidet undersøkelse omkring uke 28 og en ekstra undersøkelse omkring 12 uker etter fødselen.

Alle gangene vil vi stille deg spørsmål om din helse og intervjue deg om kostholdet ditt og din fysiske aktivitet, og kartlegge din fysiske aktivitet med et armbånd som bæres på overarmen. Vi vil også stille noen spørsmål om helseforhold og sykdom i familien, veie deg med en spesialvekt som angir fettinnholdet i kroppen, og måle hudtykkelsen med en enkel ytre målemetode.

Alle disse tre gangene må du møte fastende på grunn av de ekstra blodprøvene som skal tas sammen med rutineprøvene i svangerskapet. Det betyr at du ikke skal spise, drikke eller røyke etter kl 24 kvelden før disse timene hos oss. Rutineprøvene og noen av de andre blodprøvene vil du få svar på ved neste undersøkelse. Andre blir sendt til sykehus for nedfrysing for senere analyser. Det gjelder også urinprøvene.

Omkring uke 28 vil vi ta en blodsukkerbelastning som gjøres på følgende måte: Etter den fastende blodprøven drikker du 75 gram druesukker. Etter 2 timer tas en ny blodprøve. Det er lurt å ta med matpakke som du kan spise etterpå. Prøvene analyseres på helsestasjonen. Du får med en gang vite om du har fått svangerskapsdiabetes. Da får du ekstra oppfølging/behandling.

Du vil også bli tilbudt 3 ekstra ultralydundersøkelser for å se på barnets vekst. Etter fødselen vil vi i samarbeide med sykehuset du føder på innhente journalopplysninger fra svangerskapet om resultatene av ultralydundersøkelsene, fødselsforløpet, din helse og barnets lengde, vekt, hodeomkrets, fordeling av kroppsfett og helsetilstand. Det tas også blodprøver fra barnets navlestreng og morkake ved fødselen.

Etter fødselen ønsker vi å kartlegge hvor lenge barnet får morsmelk, og hvordan barnet vokser (lengde og vektutvikling) i barnealderen. Dette skjer ved den vanlige barnekontrollen på helsestasjonen. Vi ønsker å kunne gjøre noen tilleggsundersøkelser av barnet ved 6 og 10 års alder (kost, fysisk aktivitet og blodprøver). ***Kvinner som får påvist svangerskapsdiabetes*** vil få utført ny blodsukkerbelastning ca.3 måneder etter fødselen. Vi vil senere også innkalle dem en gang i året i 5 år, og så hvert 5. år for nye prøver for å avklare om de har fått type 2 diabetes.

Ved oppfølgingsstudiene vil vi komme tilbake med ny henvendelse med spørsmål om å delta.

Mulige fordeler og ubehag/ulemper

- Økt kunnskap om fysisk aktivitet, sunn kost og helse.
- Ekstra nøye oppfølging av de som får påvist svangerskapsdiabetes
- Blodsukkerbelastningen (uke 28 og 3 mnd etter fødsel) kan utløse kvalme
- Ingen av de andre undersøkelsene gir ubehag eller risiko utover vanlig blodprøvetakning.
- Ved blodprøver av barnet ved 6 og 10 års alder vil barnet på forhånd kunne få lokalbedøvende salve på huden.

Kapittel B - Personvern, biobank, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er journalopplysninger fra helsekort for gravide, sykehusjournal fra mors og barnets journal i forbindelse med svangerskap og fødsel hentet ut av autorisert helsepersonell, fra intervjuene om kost og fysisk aktivitet, og resultater fra de innsamlede målinger og blod- og urinprøver. For barnet ditt gjelder det opplysninger fra sykehuset fra fødsel og nyfødtperiode, og helsestasjonsdata om amming, vekstutvikling, samt tilleggsundersøkelsene om kosthold, fysisk aktivitet og blodprøver ved 6 og 10 års alder. For å finne mer ut om helsekonsekvensene av fysisk inaktivitet, overvekt og diabetes og senere helse for mor og barn, spesielt hvorfor noen får diabetes og hjerte- og karsykdom, ønsker vi å kunne hente ut opplysninger om disse diagnosene fra din journal hos fastlege og sykehus der du får behandling, og kunne koble opplysningene fra "STORK Groruddalen" med data fra Norsk Pasientregister, Norsk Diabetesregister for voksne, Reseptregisteret, Dødsårsaksregistertet og Medisinsk fødselsregister Alle som får innsyn, har taushetsplikt. Opplysninger om fars helse og forekomst av hjerte- og karsykdom og diabetes i familien vil også bli samlet inn. For at det skal være mulig å følge med din og barnets medisinske utvikling over lengre tid, slettes opplysninger og prøver først i 2030. Aker universitetssykehus ved administrerende direktør er databehandlingsansvarlig for studien.

Behandling av materiale og opplysninger hos andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at avidentifiserte opplysninger og prøver kan oppbevares og behandles hos ulike forskere og samarbeidspartnere tilknyttet prosjektet, i Norge og i utlandet. Dette er nødvendig for å oppfylle formålet med studien.
Vi vil stille samme strenge krav til beskyttelse av informasjonen til våre samarbeidspartnere, også i land med lover som ikke gir like god personvernbeskyttelse som her.

Biobank
Blod- og urinprøvene og vev fra morkake som blir tatt og informasjonen utledet av dette materialet, vil bli lagret i en forskningsbiobank ved Aker universitetssykehus. Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Prof. dr. med. Kåre Birkeland er ansvarlig for biobanken. Biobanken planlegges å vare til 2030. Etter dette vil materialet og opplysninger bli ødelagt etter interne retningslinjer.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har også rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi, prosjektleders rolle og forsikring
Studien og biobanken er finansiert gjennom forskningsmidler fra Forskningsrådet og Helse Sør-Øst. Vi vil senere kunne søke også andre kilder, som farmasøytisk industri. Prosjektleder har ingen personlige økonomiske interesser i prosjektet. Norsk pasientskadeerstatningsordning gjelder ved deltagelse i studien.

STORK Groruddalen

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)

PAPERS I–III

I

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BMC Pregnancy and Childbirth

RESEARCH ARTICLE Open Access

Vitamin D deficiency and supplementation in pregnancy in a multiethnic population-based cohort

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Abstract

Background: To investigate ethnic differences in vitamin D levels during pregnancy, assess risk factors for vitamin D deficiency and explore the effect of vitamin D supplementation in women with deficiency in early pregnancy.

Methods: This is a population-based, multiethnic cohort study of pregnant women attending Child Health Clinics for antenatal care in Oslo, Norway. Serum-25-hydroxyvitamin D [25(OH)D] was measured in 748 pregnant women (59 % ethnic minorities) at gestational weeks (GW) 15 (SD:3.6) and 28 (1.4). Women with 25(OH)D <37 nmol/L at GW 15 were for ethical reasons recommended vitamin D_3 supplementation. Main outcome measure was 25(OH)D, and linear regression models were performed.

Results: Severe deficiency (25(OH)D <25 nmol/L) was found at GW 15 in 45 % of women from South Asia, 40 % from the Middle East and 26 % from Sub-Saharan Africa, compared to 2.5 % in women from East Asia and 1.3 % of women from Western Europe. Women from South Asia, the Middle East and Sub-Saharan Africa had mean values that were −28 (95 % CI:-33, −23), −24 (−29, −18) and −20 (−27, −13) nmol/L lower than in Western women, respectively. Ethnicity, education, season and intake of vitamin D were independently associated with 25(OH)D. At GW 28, the mean 25(OH)D had increased from 23 (SD:7.8) to 47 (27) nmol/L ($p < 0.01$) in women who were recommended vitamin D supplementation, with small or no change in women with sufficient vitamin D levels at baseline.

Conclusions: Vitamin D deficiency was prevalent among South Asian, Middle Eastern and African women. The serum levels of 25(OH)D increased significantly from GW 15 to 28 in vitamin D deficient women who received a recommendation for supplementation. This recommendation of vitamin D supplementation increased vitamin D levels in deficient women.

Keywords: Vitamin D, Deficiency, Supplementation, Pregnancy, Ethnic minority

Background

Vitamin D deficiency in pregnancy is prevalent [1], especially in women with limited access to sunlight due to minimal outdoor activity or heavy use of sunscreen, cultural practices or traditional clothing, and among women with dark skin pigmentation. In Europe, vitamin D deficiency is reported to be prevalent among pregnant ethnic minority women in the Netherlands [2] and UK [3], but is also observed in the majority population [3–5]. Little is known about the prevalence of vitamin D deficiency among Asian and African pregnant women living in Northern Europe, although a few small studies from Sweden [6, 7] and Norway [8] report a high prevalence of vitamin D deficiency among Somali and Pakistani women. There are few population-based studies exploring vitamin D deficiency in pregnancy in today's multiethnic Europe, and little is known about the impact of socioeconomic status or the effect of vitamin D supplements [9, 10]. Also studies of multiethnic populations in Australia have

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uncovered maternal country of birth in Asia and Africa as risk factor of vitamin D deficiency in pregnancy [11].

Studies provide inconsistent and conflicting evidence for adverse maternal and child health outcomes related to vitamin D deficiency [11–16]. However, the current state of evidence suggests unclear benefits of routine vitamin D supplementation for most maternal or child health outcomes [17]. Most studies report results from interventions in non-deficient women. Despite the controversies related to adverse outcomes, and lack of evidence of clear benefits of routine supplementation, most Western countries recommend vitamin D supplementation during pregnancy.

The aims of this paper were to investigate ethnic differences in vitamin D levels during pregnancy, assess risk factors for vitamin D deficiency and explore the effect of vitamin D supplementation in women identified with low values during early pregnancy.

Methods

Design, setting and study population

Data are from the STORK Groruddalen project, which is a population-based, prospective cohort of 823 healthy women from 65 countries attending Child Health Clinics (CHC) for antenatal care in Groruddalen, Oslo, Norway, between May 2008 and March 2010. Groruddalen covers affluent as well as relatively economically deprived residential areas, and has a population with diverse socioeconomic status. This area was selected to ensure a high proportion of women with an ethnic minority background, and because the majority (75-85 %) of pregnant women residing in this area attend the Child Health Clinics for antenatal care. Antenatal care is free of charge in Norway and easily accessible. To facilitate inclusion of ethnic minority women, information material about the study and questionnaires were translated to Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu and Vietnamese and quality checked by bilingual health professionals. The STORK Groruddalen project has been described in detail elsewhere [18]. In short, women were eligible if they 1) lived in the district, 2) planned to give birth at one of the two study hospitals, 3) were <20 weeks pregnant, 4) could communicate in Norwegian or any of the specified languages and 5) were able to provide written consent to participate. Women with pre-pregnancy diabetes or other diseases necessitating intensive hospital follow-up during pregnancy were excluded. In total, 59 % of the included women were of ethnic minority background. The participation rate was 74 % (range: 64-83 % for ethnic groups), and the participating women were found representative for the main ethnic groups of pregnant women attending Child Health Clinics in Oslo [18]. Data from questionnaires, measurements and blood samples were collected at 15 and 28 weeks of gestation, through interviews by specially trained and certified midwives according to the study protocol, assisted by professional interpreters when needed.

Data collection and variables

Primary outcome measure

S-25-hydroxyvitamin D [25(OH)D] was analyzed by competitive radioimmunoassay (DiaSorin, Stillwater, MN, USA) at the Hormone Laboratory, Oslo University Hospital, Aker. The method measures a total value of 25(OH)D (both 25(OH)D_2 and -D_3), with intra- and inter-assay coefficients of variation 6 % and 13-16 %, respectively. The laboratory's normal reference range was 37–131 nmol/l based on the ethnic Norwegian population from the Oslo Health Study [19]. The laboratory is accredited by International Organization for Standardization and is part of the Vitamin D Quality Assessment Scheme, DEQAS. Samples were analyzed consecutively and results were sent to the participant's midwife.

In this paper, vitamin D deficiency was defined as 25(OH) D <50 nmol/L, and severe vitamin D deficiency was defined as 25(OH) D <25 nmol/L, in accordance with relevant literature [20]. Undetectable concentrations of 25(OH)D (<12 nmol/L) were replaced with "11 nmol/L" in the calculations (n = 17).

Explanatory factors

Ethnic origin was defined by the participant's mother's country of birth[18]. Ethnicity was further categorized into Western Europe (primarily Norway, Sweden and Denmark), South Asia (primarily Pakistan and Sri Lanka), Middle East (primarily Iraq, Turkey, Morocco and Afghanistan), Africa (Somalian being the largest group), East Asia (primarily Vietnam, Philippines and Thailand), and Other (primarily Poland, Russia and Kosovo). Parity was categorized as no children (nulliparous), one child (uniparous) and two or more children (multiparous). Pre-pregnancy body mass index (BMI; calculated from self-reported weight before pregnancy and height measured at inclusion) was categorized as <25 kg/m^2 and ≥25 kg/m^2. Education level was categorized as <10 years, 10–12 years and >12 years. Winter season was defined as December to May. According to National Clinical Guidelines for Antenatal Care, the recommendation of vitamin D intake during a normal pregnancy is 10 μg/day [21]. All participants were asked about their intake of vitamin D supplements including prenatal vitamins during the past two weeks at both visits, and self-reported intake was categorized as " vitamin D ≥10 μg/day" and "no or vitamin D <10 μg/day". Other variables of interest were age and gestational week at inclusion. Gestational week at inclusion was dichotomized according to the median.

The recommendation of vitamin D supplementation

Pre-planned, and according to the protocol, women with 25(OH)D less than the laboratory's lower reference range (<37 nmol/L) at gestational week 15 were provided with written information describing their 25(OH)D D concentration, and they were recommended to consult their General Practitioner (GP) for treatment. Specially, these women were provided a written note advising their GP to prescribe 20 μg (800 IU)/day vitamin D_3 for 1–3 months if 25(OH)D ranged from 12–37 nmol/L or 30 μg (1200 IU)/day vitamin D_3 for 3 months if 25(OH)D <12 nmol/L. In addition, 1 g calcium/day was recommended for both groups, and GPs were encouraged to offer follow-up measurements. Due to lack of safety evidence for the fetus and mother for higher doses, and to avoid hypercalcemia in the fetus/newborn, we used a daily dose below the Tolerable Upper Intake Level (for adults 50 μg/d (2000 IU)) when the study was performed [22]. We have no information on the exact dose of vitamin D supplements taken if self-reported intake was >10 μg/day.

Ethics

The Regional Committee for Medical and Health Research Ethics South East (Ref 2007/894) and the Norwegian Data Inspectorate approved the study protocol. Participation was based on informed, written consent.

Study sample

Of the 823 women included in the STORK Groruddalen project, 807 (98 %) had 25(OH)D concentrations measured at gestational week 15. At gestational week 28, 20 women had had an abortion or extreme premature delivery, 29 did not re-attend, and 10 women lacked a 25(OH)D value, resulting in a final sample of 748 (91 %) women with two 25(OH)D measurements in this study (Flow chart, Additional file 1: Supplementary Figure).

Statistics

Descriptive statistics are presented as frequencies, proportions, mean values and standard deviations (SD). All continuous variables were assessed for normality. In Additional file 2: Supplementary table, we report mean values for 25(OH)D for ethnic groups with ≥10 participants. Comparisons of means and proportions were tested by independent and paired t-tests and chi-square tests. Explanatory linear regression models were performed to assess the relationship between ethnicity and the concentration of 25(OH)D, both at inclusion and in gestational week 28, accounting for the following potential confounding factors: gestational week, age, parity, season, education, vitamin D supplements and pre-pregnancy BMI. Due to a non-linear relation with 25(OH)D, pre-pregnancy BMI was dichotomized. Factors with a p-value <0.2 in the univariate analysis were included in the multiple regression analyses. Interactions were examined graphically and by adding interaction terms (Western and summer vs non-Western and winter) into the models. Results are presented as regression coefficients (B) with 95 % confidence intervals (CI) and accompanied adjusted R^2. P-values <0.05 were considered statistically significant. SPSS software (Version 22, IBM SPSS statistics, NY, USA) was used for statistical analysis.

Results

Mean maternal age was 30 (SD: 4.9) years (range 19 to 45) and mean pre-pregnancy BMI 24.6 (SD: 4.8) kg/m^2. The mean gestational week was 15.4 (SD: 3.6) at inclusion and 28.8 (1.4) at the follow-up visit (Table 1). The ethnic minority women were younger, had higher parity and lower education (25 % reported no, or less than 10 years of schooling) than Western European women. A total of 23 % of ethnic minority women needed an interpreter (21 % reported "poor" or "somewhat poor" skills in the Norwegian language, while 18 % "medium" skills). Reported reasons for migrating to Norway were work or studies (9.1 %), refugees or asylum seekers (18 %) and family immigration (73 %). About two thirds of Western European and East Asian women reported using vitamin D supplements regularly at inclusion compared to 50 % of other ethnic groups.

At gestational week 28, the proportion of South Asian and Middle Eastern women who had used vitamin D supplements ≥10 μg/day over the past two weeks was higher than at gestational week 15 ($p < 0.01$ and $p < 0.05$, respectively). No change in the proportion using vitamin D supplements was observed among the other ethnic groups (Table 1). No significant differences between the study sample and the 75 excluded women were found for ethnicity, age, gestational week (both visits), parity, pre-pregnant BMI and education (data not shown).

Vitamin D status in early pregnancy at gestational week 15

The 25(OH)D concentration at inclusion ranged from <12 to 148 nmol/L, with large differences in mean values between the ethnic groups (Table 2). Mean values for countries with ≥10 participants are provided in Additional file 2: Supplementary table. The prevalence of 25(OH)D <50 nmol/L differed between the ethnic groups as follows: South Asia: 84 %, the Middle East: 79 %, Sub-Saharan Africa: 75 %, East Asia: 43 % and Western Europe: 20 %. For severe deficiency (25(OH)D <25 nmol/L), corresponding numbers were: South Asia: 45 %, the Middle East: 40 %, Sub-Saharan Africa: 26 %, East Asia: 2.5 % and

Table 1 Characteristics of the total cohort of pregnant women at inclusion and at gestational week 28 stratified by geographic region. Numbers are frequencies (%) and means (SD)

	Total	Western Europe[a]	South Asia	Middle East	Sub-Saharan Africa	East Asia	Other
	n = 748	n = 304	n = 189	n = 113	n = 51	n = 40	n = 51
	100 %	41 %	25 %	15 %	6.8 %	5.3 %	6.8 %
Pre-pregnancy maternal status							
Years of maternal age; mean (SD)	29.9 (4.9)	30.9 (4.5)	28.7 (4.5)	29.6 (5.5)	28.1 (5.2)	31.1 (4.5)	29.3 (5.1)
Parity; n (%)							
Para 0	340 (46)	156 (51)	78 (41)	39 (35)	22 (43)	17 (42)	28 (55)
Para 1	259 (34)	113 (37)	63 (33)	39 (35)	11 (22)	16 (40)	17 (33)
Para 2	149 (20)	35 (12)	48 (25)	35 (30)	18 (35)	7 (18)	6 (12)
Education level; n (%)[b]							
<10 years	119 (16)	10 (3.3)	33 (18)	41 (36)	22 (43)	8 (20)	5 (9.8)
10-12 years	296 (40)	93 (30)	95 (50)	51 (45)	22 (43)	16 (40)	19 (37)
>12 years	327 (44)	199 (66)	60 (32)	19 (17)	7 (14)	16 (40)	26 (51)
Pre-pregnancy BMI[b] (kg/m2); mean (SD)	24.6 (4.8)	24.6 (4.8)	23.7 (4.1)	25.8 (5.0)	26.1 (6.1)	22.2 (3.4)	24.9 (5.4)
Status at inclusion							
Gestational week; mean (SD)	15.4 (3.6)	14.5 (2.4)	15.9 (4.1)	15.6 (3.3)	17.9 (5.4)	16.4 (4.3)	15.5 (3.4)
Season of blood sample; n (%)							
Winter	395 (53)	158 (52)	92 (49)	70 (62)	32 (63)	22 (55)	21 (41)
Vitamin D supplements; n (%)[b]							
No or <10 μg daily past two weeks	307 (41)	104 (34)	93 (49)	55 (49)	25 (49)	12 (30)	18 (35)
Status at gestational week 28							
Gestational week; mean (SD)	28.8 (1.4)	28.7 (1.3)	28.7 (1.4)	29.0 (1.6)	29.0 (1.5)	28.7 (1.2)	29.0 (1.7)
Weight gain (week 28 minus 15); mean (SD)	6.6 (3.2)	6.7 (2.7)	6.5 (3.3)	6.7 (3.6)	4.6 (3.0)	6.2 (2.5)	8.0 (3.9)
Season of blood sample; n (%)							
Winter	410 (55)	178 (59)	97 (51)	65 (57)	28 (55)	17 (57)	25 (49)
Vitamin D supplements; n (%)[b]							
No or <10 μg daily past two weeks	243 (33)	115 (38)	41 (22)	37 (33)	20 (40)	14 (35)	16 (31)

Notes:
Countries with ≥10 individuals are listed: 304 women from Western Europe, primarily from Norway ($n = 278$), 189 women from South Asia, primarily from Pakistan $n = 120$), Sri Lanka ($n = 56$) and India ($n = 12$), 113 women from the Middel East, primarily from Iraq (n = 34), Morocco ($n = 27$), Turkey (n = 25), Afghanistan ($n = 12$), 51 women from Sub-Saharan Africa, primarily from Somalia ($n = 32$), 40 women from East Asia, primarily Vietnam ($n = 17$), Philippines ($n = 12$).
[a]Including 3 women from USA and Canada
[b]Incomplete data on the variables because of missing values for 6–12 women

Western Europe: 1.3 %, representing 20 % of the total cohort (Fig. 1).

In early pregnancy, the values of 25(OH)D differed between the ethnic groups and remained significant after adjustment for age, parity, season, education and intake of vitamin D supplements (Table 3). Women from South Asia, the Middle East and Sub-Saharan Africa had mean values that were −28 (95 % CI: −33, −23), −24 (−29, −18) and −20 (−27, −13) nmol/L lower than in Western European women, respectively. In addition, education, intake of vitamin D supplements and season were independently associated with 25(OH)D concentrations at inclusion. The effect of season on 25(OH)D differed by ethnicity (interaction term, $p < 0.01$). Western European women had a higher concentration of 25(OH)D during summer compared to winter, while no seasonal difference was observed among ethnic minority women, and their mean values were lower than Western Europeans.

Vitamin D status at gestational week 28

At the beginning of the third trimester, the prevalence of 25(OH)D <50 nmol/L among the largest ethnic minority groups was lower than at study inclusion: South Asia: 62 %, the Middle East: 58 % and Sub-Saharan Africa: 63 %. The prevalence of 25(OH)D <25 nmol/L was also lower: South Asia: 17 %, Middle East: 15 %, Sub-Saharan Africa: 20 % (Fig. 1).

Mean 25(OH)D values were −17 (95 % CI: −23, −11), −10 (−16, −2.9) and −12 (−20, −3.1) nmol/L lower in

Table 2 Descriptive vitamin D at inclusion (gestational week 15) and at gestational week 28. Crude mean (SD) Vitamin D [25(OH)D in nmol/l] levels according to potential explanatory factors

	At inclusion *n* = 748		At gestational week 28 *n* = 748	
	Mean	(SD)	Mean	(SD)
Overall mean 25(OH)D	50	(27)	59	(29)
Age at inclusion				
30 years	47	(25)	55	(27)
>30 years	54	(28)	62	(30)
Parity (Para 0 ref)	53	(26)	61	(29)
Para 1	52	(28)	59	(27)
Para 2	42	(25)	52	(30)
Western Europe (ref)	69	(24)	72	(28)
South Asia	32	(19)	46	(23)
Middle East	34	(20)	51	(29)
Sub-Saharan Africa	38	(18)	45	(25)
East Asia	51	(17)	53	(19)
Other	56	(21)	63	(26)
Season of blood sample				
Summer	56	(29)	60	(29)
Winter	46	(24)	57	(27)
Education level (>12 years ref)	60	(27)	67	(27)
10-12 years	46	(25)	56	(29)
<10 years	37	(20)	44	(23)
Vitamin D supplements				
10 μg [a]	57	(26)	61	(28)
No or <10 μg	42	(26)	53	(29)
Pre-pregnancy BMI; kg/m2 (normal weight (<25) ref)	51	(27)	59	(29)
Overweight (25/<30)	51	(27)	61	(31)
Obesity (30)	48	(24)	54	(24)

[a]Intake of ≥10 μg vitamin D daily past two weeks

South Asians, Middle Easterners and Sub-Saharan Africans compared with Western Europeans after adjustments for gestational week at inclusion, age, parity, season, education and vitamin D supplements (Table 3). In addition, age, parity, education, intake of vitamin D supplementation and gestational week at inclusion were independently associated with 25(OH)D concentrations. The effect of season on 25(OH)D differed by ethnicity (interaction term, $p < 0.01$) at gestational week 28.

A sensitivity analysis to evaluate the effect of the interaction term was performed. When excluding the geographic region*season interaction term from the multiple analyses (Table 3), the coefficients for ethnic minority groups and season were reduced by the same amount as the interaction-coefficient, while the coefficients for the remaining factors were about the same.

Vitamin D status in women who were recommended supplementation in early pregnancy

In total, 258 women (35 %) had values <37 nmol/L at inclusion and were recommended to consult their GPs for supplements. Only 37 % of these women reported an intake of ≥10 μg/day of vitamin D supplements, but at gestational week 28, this proportion had increased to 73 % ($p < 0.01$). Among the 67 women reporting no or <10 μg/day at this time point, 11 women had 25(OH)D >50 nmol/L and 26 women (10 % of the group recommended supplementation and 3.5 % of the total cohort), had 25(OH)D <25 nmol/L. In parallel to the increased use of supplements in this group, the mean 25(OH)D increased from 23 (SD:7.8) to 47 (27) nmol/L ($p < 0.01$). No changes in mean 25(OH)D were observed among women with baseline values >50 nmol/L, while a slight increase in mean 25(OH)D was observed in women with baseline values ranging from 37–50 nmol/L. Corresponding results are presented for Western European women (Fig. 2a) and the merged ethnic minority groups (Fig. 2b). The mean change in 25(OH)D from GW 15 to 28 was 24 nmol/L in the group recommended supplementation compared to 0.1 nmol/L in the group with levels ≥37 nmol/L ($p < 0.01$).

Discussion

Main findings

In this cohort study we found a high prevalence of vitamin D deficiency (<50 nmol/L) in early pregnancy among women from South Asia, Middle East and Sub-Saharan Africa, and severe deficiency (<25 nmol/L) was prevalent among women from these regions. Independent risk factors for low 25(OH)D values in early pregnancy included ethnic origin from South Asia, the Middle East and Sub-Saharan Africa, low intake of supplements, low education, and examination during winter. Among women who were recommended to consult their GPs for supplementation, use of supplements and levels of 25(OH)D increased substantially more than in women with values ≥37 nmol/L who not were exposed to this recommendation.

Strengths and limitations

The major strength of the study is that we followed a large number of healthy women representative for the main ethnic groups of pregnant women in Oslo through pregnancy. The questionnaires were translated to eight languages and data collection methods were adapted to facilitate inclusion of ethnic minorities and even illiterate women, who are often excluded in research [18]. Professional interpreters were used to ensure the quality of the

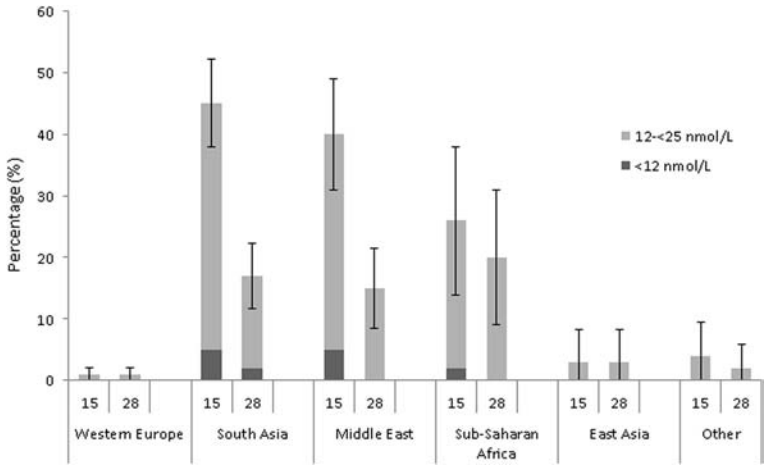

Fig. 1 Proportions of participants with levels of 25(OH)D 12- < 25 nmol/L and <12 nmol/L at gestational week 15 and 28

interview administered questionnaire data. We were able to include a relatively wide range of explanatory factors, and we collected data at two time points in pregnancy. The blood samples were analyzed at the same laboratory with standardized methods.

However, there are also weaknesses. This was not a randomized, controlled trial, but was evaluated by a pre-post test design. We do not directly know the impact of the letter from the study personnel to the GPs, nor do we know the participants' level of adherence to the recommendations from the GPs. However, 73 % reported use of ≥10 μg/day of vitamin D supplements at the post-test, and only 3.5 % still had severe deficiency, compared to 20 % at inclusion. We lack information on other variables affecting the concentration of 25(OH)D, including the degree of concealing clothes, skin pigmentation and sunlight exposure.

Interpretation

Our findings are in line with others confirming widespread vitamin D deficiency during pregnancy among ethnic minorities [2, 3, 11, 23, 24], although some studies from Northern Europe have found a comparatively higher prevalence and more severe deficiency than observed in our study [6, 25]. Recent studies from the same part of Oslo may have increased awareness of vitamin D deficiency among health personnel [26–28], which may have contributed to the somewhat lower prevalence of vitamin D deficiency in ethnic minorities in our study. However, direct comparison of 25(OH)D values between studies are hampered by different methodologies such as inconsistent definitions of vitamin D deficiency, laboratory measurements and degree of adjustment for possible confounders.

Most studies that we identified were cross-sectional, and few adjusted for intake of vitamin D supplements, education, parity and seasonal variance [5, 29]. At high latitude, seasonal variance is an important explanatory factor, as the sun is not capable of producing vitamin D by skin radiation during winter time [30]. Some ethnic minority groups have other traditions of sun exposure than Western European women. However, we did not identify other studies from Europe testing for the interaction of ethnicity and season, while no interaction was found in a study from the US [31]. We found that low education was an independent risk factor for low values of 25(OH)D, but did not identify other studies from Europe which investigated education as an explanatory factor, although one study from the Netherlands found that less educated women had lower 25(OH)D levels compared to high educated women[32]. Our data also indicated that low self-reported intake of vitamin D supplements was an independent risk factor for vitamin D deficiency, also found in an Irish study [3]. In contrast to several prior studies, BMI was not a significant risk factor in our sample [5, 11, 33].

The debate about the optimal dose of vitamin D supplementation during pregnancy is ongoing. Guidelines from Scandinavia and UK recommend all pregnant women supplement intake with 10 μg (400 IU) vitamin D daily to prevent vitamin D deficiency [21, 34, 35]. The guidelines from the Institute of Medicine (IOM)[36], the Endocrine Society Clinical Practice [37], the WHO [38] and the Canadian Pediatric Society [39] differ. There is no consensus of the optimal concentration of 25(OH)D in pregnancy [40, 41]. There is no doubt that low infant 25(OH)D increases the risk of skeletal diseases such as rickets and hypocalcemia, but the effect of maternal deficiency on the fetus is not clear. Concerns about the

Table 3 Linear regression analysis with vitamin D [25(OH)D] at inclusion and gestational week 28 as dependant variables

	At inclusion									At gestational week 28								
	Univariate analysis					Multiple analysis n = 735, R^2 adj. = 0.46				Univariate analysis					Multiple analysis n = 730, R^2 adj. = 0.24			
Independent variable	R^2 adj.	B	95 % CI			B	95 % CI			R^2 adj.	B	95 % CI			B	95 % CI		
			Lower	Upper			Lower	Upper				Lower	Upper			Lower	Upper	
Gestational week at inclusion (<15 ref)	−0.001									0.01								
15		−0.56	−4.4	3.3							**−6.4**	**−10**	**−2.3**	**	**−4.6**	**−8.3**	**−0.92**	*
Age at inclusion	0.03	**0.94**	**0.55**	**1.3**	**	0.14	−0.21	0.49		0.03	**1.1**	**0.64**	**1.5**	**	**0.70**	**0.26**	**1.1**	**
Parity (para 0 ref)	0.02									0.01								
Para1		−1.2	−5.4	3.1		0.24	−3.1	3.6			−2.8	−7.4	1.8		**−4.4**	**−8.7**	**−0.22**	*
Para 2		**−11**	**−17**	**−6.3**	**	−3.2	−7.6	1.3			**−9.3**	**−15**	**−3.8**	**	−5.4	−11	0.25	
Geographic region (Western Europe ref)	0.38									0.16								
South Asia		**−37**	**−40**	**−33**	**	**−28**	**−33**	**−23**	**		**−26**	**−31**	**−21**	**	**−17**	**−23**	**−11**	**
Middle East		**−34**	**−39**	**−30**	**	**−24**	**−29**	**−18**	**		**−21**	**−26**	**−15**	**	**−9.5**	**−16**	**−2.9**	**
Sub-Saharan Africa		**−31**	**−37**	**−25**	**	**−20**	**−27**	**−13**	**		**−26**	**−34**	**−19**	**	**−12**	**−20**	**−3.1**	**
East Asia		**−17**	**−24**	**−10**	**	**−11**	**−18**	**−3.9**	**		**−19**	**−28**	**−11**	**	**−11**	**−20**	**−1.6**	*
Other		**−13**	**−19**	**−6.4**	**	**−7.6**	**−14**	**−0.90**	*		**−9.0**	**−17**	**−1.3**	*	−1.4	−9.6	6.9	
Season (Summer ref)	0.03									0.01								
Winter		**−9.9**	**−14**	**−6.1**	**	**−5.2**	**−8.9**	**−1.4**	**		**−5.7**	**−9.8**	**−1.6**	**	−1.3	−6.1	3.4	
Geographic region*Season[a]						**−11**	**−16**	**−4.8**	**						**−15**	**−22**	**−7.4**	**
Education level (>12 y ref)	0.11									0.08								
10-12 year		**−14**	**−18**	**−10**	**	**−3.7**	**−7.1**	**−0.30**	*		**−11**	**−15**	**−6.8**	**	−1.8	−6.1	2.5	
<10 year		**−23**	**−28**	**−17**	**	**−5.2**	**−10**	**−0.31**	*		**−23**	**−29**	**−17**	**	**−8.6**	**−15**	**−2.5**	**
Vitamin D supplements (10μgb ref)	0.08									0.02								
No or <10 μg		**−15**	**−19**	**−11**	**	**−11**	**−14**	**−7.7**	**		**−8.2**	**−13**	**−3.8**	**	**−9.8**	**−14**	**−5.8**	**
Pre-pregnancy BMI (<25 kg/m2ref)	−0.001									−0.001								
25 kg/m2		−0.76	−4.7	3.2							−0.11	−4.4	4.2					

[a]The effect of season on 25(OH)D differed by ethnicity: the interaction term is "1" for records with both non-Western and winter and "0" for Western and summer (ref)
[b]Intake of ≥10 μg vitamin D daily past two weeks
Bold numbers indicate $p < 0.05$ (*$p < 0.05$, ** $p < 0.01$)

impact of low 25(OH)D concentrations during pregnancy on fetal development is present, as low levels have been associated with preterm birth, low birth weight, bone mass and postnatal calcium concentrations, as well as preeclampsia and gestational diabetes in the mother [11, 42].

Several studies among pregnant women have showed a marked increase in 25(OH)D with daily supplements of vitamin D [11, 24, 43, 44]. Although there may be changes to the pharmacokinetics of 25(OH)D during pregnancy, such as increased binding proteins and fluid redistribution, most studies report that 25(OH)D concentration is relatively constant, at least during the first two trimesters [4, 45]. However, some evidence suggests vitamin D binding protein may increase and the free fraction of 25(OH)D may decrease [46, 47].

In women who were recommended daily vitamin D supplements of 20 μg or 30 μg due to low values in early pregnancy, we observed an increase in self-reported use of supplements at the follow-up visit. We similarly observed a substantial increase in 25(OH)D concentrations and a reduced prevalence of 25(OH)D <25 nmol/L. The small increase of 25(OH)D observed among women with a slight deficiency at baseline who did not receive the recommendation, may be related to usual practices in Norway of routinely recommending a daily intake of 10 μg vitamin D as part of antenatal care [21]. No

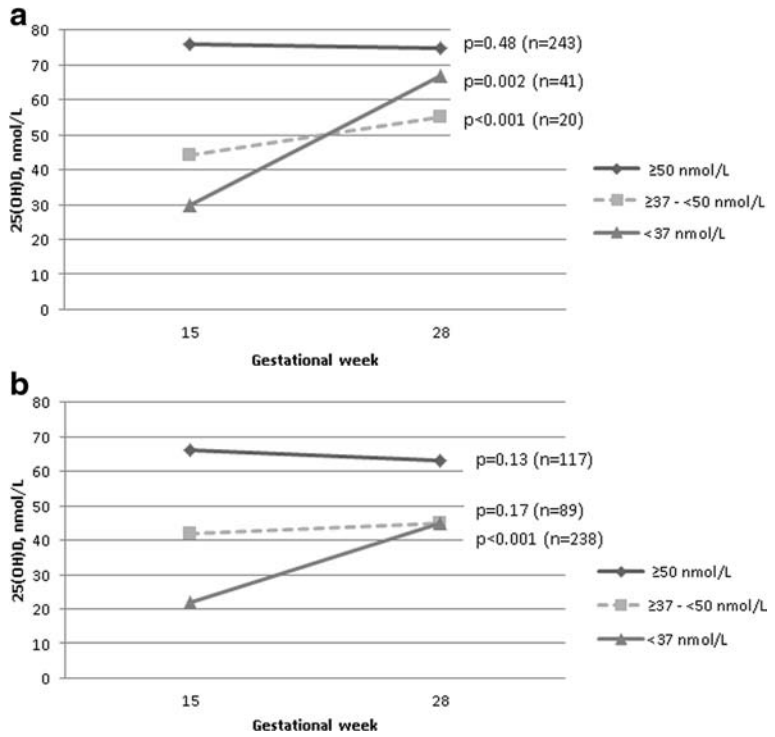

Fig. 2 a. Change in unadjusted mean 25(OH)D of Western European women at gestational week 15 and 28 - stratified for baseline levels (paired t-test). Women with <37 nmol/L at baseline were recommended 20 μg or 30 μg vitamin D daily. **b**. Change in unadjusted mean 25(OH)D of ethnic minority women at gestational week 15 and 28 - stratified for baseline levels (paired t-test). Women with <37 nmol/L at baseline were recommended 20 μg or 30 μg vitamin D daily

similar increase was observed among ethnic minority women with a slight deficiency, probably indicating inadequate delivery of the message or less compliance in these groups. Compared with no change or a small increase in 25(OH)D concentrations in women with adequate levels or mild vitamin D deficiency, this differential change may indicate a beneficial effect of the recommendations. However, it should be noted that severe vitamin D deficiency was still found in 15-20 % of the high risk groups. Although the results must be interpreted with caution because we did not conduct a randomized controlled trial, the observed increase in 25(OH)D levels in our study is unlikely to be attributable to physiological changes during pregnancy or regression to the mean only. Supplementation with a higher dose of vitamin D than 20 μg or 30 μg would likely be sufficient to achieve acceptable 25(OH)D concentration in pregnancy.

Conclusion

We found that vitamin D deficiency was prevalent among South Asian, Middle Eastern and African women in early pregnancy. Ethnic minority background, low intake of supplements, low education and winter season were independent risk factors for vitamin D deficiency. After identifying participants with low 25(OH)D values at study inclusion, and recommending treatment with daily moderate doses of vitamin D, the daily intake of supplements significantly increased and the prevalence of severe vitamin D deficiency was substantially reduced. This cost-effective, and easy-to-administer recommendation likely contributed the most to the improved vitamin D status later in pregnancy for these women.

Additional files

Additional file 1: Supplementary figure. Flow-chart. (TIF 64 kb)
Additional file 2: Supplementary table. (XLSX 11 kb)

Abbreviations

25(OH)D: Serum-25-hydroxyvitamin D; BMI: body mass index; CHC: Child Health Clinics; DEQAS: Vitamin D Quality Assessment Scheme; GP: General Practitioner; GW: Gestational week; IOM: Institute of Medicine; IU: International Units; R^2: Adjusted R-square; SD: Standard deviation; SPSS: Statistical package for the social science; UK: United Kingdom; US: United States of America; WHO: World Health Organization.

Competing interests

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Authors' contributions
AKJ initiated the STORK Groruddalen study in close collaboration with KIB. LS participated in data collecting. ÅRE and AKJ designed the sub-study. ÅRE prepared the first version of the manuscript. AKJ, RSF, KVK, LS, KIB and PL contributed to the discussion and results. ÅRE and RSF performed the statistical analyses. All authors have revised the manuscript and approved the final version.

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II

Vitamin D, gestational diabetes and measures of glucose metabolism in a population-based multi-ethnic cohort

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Abstract

Objective: We explored associations between maternal 25-hydroxyvitamin D [25(OH)D] status during pregnancy and gestational diabetes (GDM) and other measures of glucose metabolism.

Methods: We analyzed 25(OH)D at 15 and 28 gestational week (GW) in 745 multi-ethnic pregnant women attending antenatal care units in Oslo, Norway between 2008 and 2010. GDM was diagnosed with a 75 g oral glucose tolerance test at 28 GW. Separate regression analyses were performed to investigate associations between 25(OH)D and GDM and measures of glucose metabolism.

Results: A higher proportion of ethnic minority women had GDM ($p<0.01$) and low 25(OH)D ($p<0.01$) compared to Europeans. In logistic regression analyses 25(OH)D <50 nmol/L was associated with GDM after adjusting for age, parity, education and season (OR 1.6; 95% CI 1.1-2.2). After additional adjustments for variables reflecting fat mass (skinfolds or BMI) and ethnicity, the association disappeared with ethnicity having a much stronger effect than the adiposity variables. We got similar results exploring effects on other measures of glucose metabolism, and when change in 25(OH)D from inclusion to 28 GW was taken into account.

Conclusions: Vitamin D deficiency was not associated with GDM or glucose metabolism in a multi-ethnic population-based study, after adjustments for confounding factors, in particular ethnicity.

Abbreviations:

25(OH)D: 25-hydroxyvitamin D

BMI: body mass index

FPG: fasting plasma glucose

DAG: Directed acyclic graph

GDM: gestational diabetes mellitus

GW: gestational week

HOMA: homeostatis model assessment

HOMA-IR: homeostatis model assessment of insulin resistance

HOMA-B: homeostatis model assessment of β-cell function

PG: plasma glucose

Introduction

Although the role of vitamin D in calcium metabolism and bone health is undisputed, other long term health consequences of low vitamin D are still debated (1, 2). During the last decade, many observational studies have reported an association between low levels of vitamin D and impaired glucose metabolism and type 2 diabetes (1, 3), although results from trials so far have not confirmed a causal relationship (1, 4). Observational studies have indicated that vitamin D deficiency may be a modifiable risk factor also for gestational diabetes mellitus (GDM) (5), and some studies have found associations with other measures of glucose metabolism in pregnancy (6). Several reviews and meta-analyses have recently assessed the relation between vitamin D and GDM in observational studies (7-12). A modest increase in odds of GDM has been found, with a range from 1.38 to 1.61 in women with low levels of vitamin D (5). Subgroup analyses have found differences based on countries, analytical methods for vitamin D, definition of GDM, maternal age, sample size, adjustment for confounders, and study quality (8), confirming the complexity of interactions among individual, lifestyle, and geographical factors (5).

Vitamin D deficiency in pregnancy is widespread (13), and in Europe, women in ethnic minority groups from South Asia, The Middle East and South Sahara Africa are at highest risk (14-16). Possible biological mechanisms of the association between vitamin D and GDM are through effects on insulin-sensitive tissues, calcium pool dysregulation in the pancreas, genetic variations or inflammation (5, 6). In addition, β-cells may directly convert vitamin D into its active form as both vitamin D receptor and the 1α-hydroxylase enzyme have been found expressed in pancreatic islet (17). During pregnancy, irrespective of the pre-pregnant level, insulin resistance increases about 50-60% (18, 19), but is exaggerated by excessive gestational weight gain. GDM reflects both increased insulin resistance and β-cell

dysfunction, and both these components have been found to be associated with vitamin D levels (6). Further, we have previously found a high prevalence of both vitamin D deficiency (14), GDM (20) and measures of glucose metabolism, especially in ethnic minority groups, making us capable of exploring relations between vitamin D deficiency, ethnicity and GDM. Therefore, in the present study we aimed to assess associations between maternal 25-hydroxyvitamin D (25(OH)D) and GDM and measures of glucose metabolism, insulin resistance and β-cell function, before and after adjusting for potentially confounding factors.

Materials and Methods

Design, setting and study population

Data are from a population-based, prospective cohort of 823 presumably healthy women attending Maternal and Child Health Clinics for antenatal care in Groruddalen, Oslo, Norway, between May 2008 and March 2010 (The STORK Groruddalen study) (21). The majority (75–85 %) of pregnant women residing in this area, situated at a latitude of 60°N, attend the Child Health Clinics for antenatal care. The study design has been described in detail elsewhere (21). In short, information material and questionnaires were translated into Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu and Vietnamese and quality checked by bilingual health professionals. Women were eligible if they (1) lived in the district, (2) planned to give birth at one of the two study hospitals, (3) were in <20 gestational week (GW), (4) were not suffering from diseases necessitating intensive hospital follow-up during pregnancy, (5) could communicate in Norwegian or any of the specified languages and (6) were able to provide written consent. In total, 59% of the included women had an ethnic minority background. The participation rate was 74%, and the participating women were found representative of the main ethnic groups (20). Maternal data were collected at 15 and 28 GW, through interviews by study personnel, assisted by professional interpreters when

needed. Clinical measurements and blood samples were collected according to the study protocol.

Ethics

The Regional Committee for Medical and Health Research Ethics for South-Eastern Norway (Ref. REK 2007/894) and the Norwegian Data Inspectorate approved the study protocol. Participation was based on informed written consent.

Study sample

Of the 823 women included in the STORK Groruddalen project at 15 GW, 772 met at 28 GW and 768 of these women had valid data on GDM status by the WHO_{2013} criteria. Thirteen women were excluded because of missing data on 25(OH)D at inclusion (15 GW), and ten women from South or Central America were excluded due to low numbers from this geographic region, leaving a study sample of 745 (91 %) women (flow chart, Supplementary figure S1). For secondary outcomes, the sample size was 731 due to some missing values for C-peptide.

Variables

Outcome variables

The primary outcome in this particular analysis was GDM by the WHO_{2013} criteria (fasting plasma glucose (FPG) ≥5.1 or 2-h glucose ≥8.5 mmol/L) by vitamin D status (20, 22). We used a modified version of the WHO_{2013} criteria as 1-hour PG ≥10 mmol/L was not collected. A standard 75 g oral glucose tolerance test was performed at 28 GW (20) and venous blood glucose was measured on site with a plasma calibrated HemoCue 201+ (Angelholm, Sweden).

Secondary outcome variables were FPG, 2-hour PG, insulin resistance (measured by homeostatis model assessment of insulin resistance (HOMA-IR)), β-cell function (HOMA-B) and fasting serum insulin and C-peptide, all measured at the follow-up visit at 28 GW (19). C-peptide and insulin were measured at the Hormone Laboratory, Oslo University Hospital, by non-competitive immunofluorometric assays (DELFIA, PerkinElmer Life Sciences, Wallac Oy, Turku, Finland). HOMA-IR and HOMA-B were estimated by the Oxford University HOMA Calculator 2.2 from the glucose and C-peptide concentrations (23). Plasma glucose values used in the calculations of homeostatic model were measured at the Akershus University Hospital from venous blood on gel tubes, (Vitros 5.1 FS, Ortho Clinical Diagnostics, slide adapted colorimetric method).

Main exposure variable

Serum 25(OH)D was analysed by competitive RIA (DiaSorin) at the Hormone Laboratory, Oslo University Hospital at 16 and 28 GW. The method measures total 25(OH)D (both 25(OH)D_2 and D_3), with inter-assay coefficients of variation (CV) 13-16%. The laboratory is accredited by the International Organization for Standardization and is part of the Vitamin D Quality Assessment Scheme, DEQAS. Concentrations of 25(OH)D <12 nmol/L were replaced with '11 nmol/L' in the calculations (n = 17), to not overestimate the effect of low vitamin D status. The laboratory's reference range was 37–131 nmol/L based on the ethnic Norwegian population from the Oslo Health Study (24). Pre-planned, and according to the protocol, women with 25(OH)D less than the laboratory's lower reference range (<37 nmol/L) at 15 and 28 GW were provided written information about their 25(OH)D concentration, and recommended to consult their general practitioner for treatment (14).

Confounders

We performed a search of the literature for relevant confounders', set up a Directed acyclic graph (DAG) and selected variables available in our cohort. Maternal age at inclusion was self-reported. Parity was categorised as nulliparous, uniparous or multiparous (≥2), referring to status before the current pregnancy. Education level was categorised as completed primary education or less (<10 years), completed high school education (10-12 years) and completed ≥ 4 years college/university education. Season for 25(OH)D measurements at inclusion (15 GW) was categorised as summer (June to November) and winter (December to May) (14). Specially trained study personnel performed maternal anthropometric measurements at 15 and 28 GW (21). Each measurement was taken twice and the mean used. We here report "sum of skinfolds", which is the sum of the triceps, the subscapular and the supra-iliac skinfold. Change in sum of skinfolds was calculated as the difference between "sum of skinfolds" at 15 and 28 GW. Ethnic origin was defined by the pregnant participant's mother's country of birth (25). Ethnic origin was further categorised as Europe (primarily from Norway and Sweden), and ethnic minority women, consisting of South Asia (primarily from Pakistan and Sri Lanka), Middle East including North Africa (primarily Turkey, Iraq, Afghanistan and Morocco), South Saharan Africa (primarily from Somalia, Eritrea and Ethiopia), and East Asia (primarily from Vietnam and the Philippines). Pre-pregnancy BMI was calculated from self-reported weight before pregnancy and height measured at inclusion. Weight gain was calculated as difference between self-reported pre-pregnant weight and measured weight at 28 GW. Dietary clusters were derived from four clusters reported earlier (26) and dichotomized as healthy (cluster 4) and unhealthy (cluster 1,2 and 3).

Statistical analyses

Descriptive statistics are presented as frequencies with proportions, mean values with standard deviations or 95% confidence intervals, and medians with interquartile range. All

continuous response variables were assessed for normality. Non-parametric correlations coefficients between 25(OH)D at inclusion and secondary outcomes, assessed at 28 GW, were analysed. Differences between GDM and non-GDM women were tested by t-tests for continuous variables, and chi-square test or Fischer's exact test for categorical variables. Logistic regression analyses were performed to investigate associations between 25(OH)D and GDM. Separate generalised linear models were performed to assess the relationship between the concentration of 25(OH)D and the secondary outcomes found significant in the correlation analysis (FPG, HOMA-IR, fasting insulin and C-peptide). Maternal 25(OH)D was analysed as a continuous variable, and categorised according to deficiency status (<50 nmol/L or ≥50 nmol/L). As treatment was recommended when 25(OH)D <37 nmol/L, we further categorised the 25(OH)D status during pregnancy: consistently sufficient level (≥37nmol/L at 15 and 28 GW), consistently deficient level (<37nmol/L at 15 and 28 GW), increasing level (<37nmol/L at 15 GW and ≥37nmol/L at 28 GW) and decreasing level (≥37nmol/L at 15 GW and <37nmol/L at 28 GW). Guided by the DAG (Supplementary figure 2) we chose to account for the following *potential* confounders in the regression analyses: age, parity, education, season for measurement of 25(OH)D at 15 GW, sum of skinfolds at 15 GW, change in skinfolds from 15 GW to 28 GW and geographic origin/ethnicity. Interactions between 25(OH)D and season and between 25(OH)D and ethnicity, were examined graphically and by adding interaction terms into the models. We performed sensitivity analysis including pre-pregnant BMI and weight gain from 15 to 28 GW instead of "sum of skinfolds" at inclusion and change in "sum of skinfolds" to explore the impact of different measures of adiposity. We also included the variable of dietary clusters in the final model as a sensitivity analysis. As insulin, C-peptide and HOMA-IR values were skewed, these variables were log-transformed, and we repeated the regression analyses with these variables. Results from regression analysis are presented as odds ratio (OR) and coefficients (β) with

95% CI. P-values <0.05 were considered statistically significant. SPSS software (version 22; IBM SPSS Statistics) and Stata/Se14.1 were used for statistical analysis.

Results

Sample characteristics for the total cohort are presented in Table 1 and stratified by ethnic groups in Supplementary Table 1. Age, sociodemographic and anthropometric variables, the prevalence of GDM and 25(OH)D levels differed by ethnicity. The proportion with vitamin D deficiency (25(OH)D <50 nmol/L) was significantly higher among women with GDM than among non-GDM women (60% vs. 49%, p<0.01) (Table 1). Similarly, the proportion with severe deficiency (25(OH)D <25 nmol/L) tended to be higher among GDM women (Supplementary Table 2). At 28 GW the proportion with 25(OH)D <50 nmol/L was reduced, but differences between GDM and non-GDM women remained significant (Supplementary Table 2). A higher proportion of women with consistently vitamin D deficiency and with levels increasing from low to sufficient were found among GDM women compared to non-GDM women (both p< 0.01) (Table 1). A higher proportion of ethnic minority women had GDM (Figure 1a) and low 25(OH)D (Figure 1b) compared to European women. In addition, a higher proportion of vitamin D deficient women had GDM compared with women with consistently sufficient level of vitamin D during pregnancy (Figure 2).

In univariate analyses, vitamin D deficiency (<50 nmol/L) at 15 GW and the categories consistently deficient and increasing of vitamin D status during pregnancy, were significantly associated with GDM, but analysed as a continuous variable, 25(OH)D was not significantly associated with GDM (p=0.07). Significant inverse correlations were found between 25(OH)D in early pregnancy and FPG, HOMA-IR, fasting insulin and fasting C-peptide, but not with HOMA-B or 2-hour PG (Supplementary Table 3).

Possible confounders for the relation between 25(OH)D and GDM are presented in Table 1. After adjustments for age, parity, education and season, vitamin D deficiency was still associated with GDM (Model 1; OR 1.6; 95% CI 1.1-2.2) (Table 2). The OR was slightly reduced and the association was no longer significant after additional adjustments for "sum of skinfolds" and change in "sum of skinfolds" (Model 2). Including ethnicity into the model, the OR was even more attenuated (Model 3). Similar, we found no association with GDM using vitamin D status during pregnancy after adjustments for confounders (Table 2). Based on the correlation analyses, we performed linear regression models for FPG, HOMA-IR, fasting insulin and C-peptide (Table 3). All significant associations present in unadjusted analyses and Model 1 disappeared after adjustments for confounders, with ethnicity having a much stronger effect than the adiposity variables.

Sensitivity analyses

Using the same approach, but adjusting for pre-pregnant BMI and weight gain from 15 to 28 GW instead of "sum of skinfolds" at 15 GW and change in "sum of skinfolds" in Model 2, the association was still significant (results not shown). Including dietary clusters into the models had no effect on the estimates. Using the log-transformed outcome variables in the regression models, we found exactly the same pattern of associations.

Discussion

In this population-based multi-ethnic cohort of pregnant women with a high proportion with vitamin D deficiency during the first and second trimester of pregnancy, we found that the crude prevalence of vitamin D deficiency was higher in women with GDM compared to normoglycemic women. We also found significant inverse correlations between 25(OH)D in

early pregnancy and FPG, HOMA-IR, fasting insulin and fasting C-peptide. However, in fully adjusted regression models, taking into account a number of possible confounders, low levels of 25(OH)D did not predict the development of GDM or deterioration in glucose metabolism observed from 15 to 28 GW.

Strengths of the present study include its population-based longitudinal design, the high attendance rate with minor loss to follow-up, and the relatively large sample size in a multi-ethnic European context. We also performed universal screening for GDM in 28 GW, and assessed GDM by two definitions. A broad data set was collected that made us able to explore relations between 25(OH)D and several measures of glucose metabolism, and we adjusted for a range of possible confounders after drawing a DAG. Fore ethical reasons, women with vitamin D <37 nmol/L were recommended vitamin D supplementation. As the main exposure variable 25(OH)D was measured at two time points in pregnancy, we were able to describe vitamin D levels during the first two trimesters (categories), where those who were recommended supplements can be followed. We measured 25(OH)D with standardized methods at the same high quality laboratory, and half of the sample had vitamin D deficiency, many with severe deficiency.

The main limitation of our study is that the "gold standard" methods to quantify insulin resistance and β-cell function was not feasible in our primary care setting. The HOMA-indexes are surrogate measures of insulin resistance and β-cell function estimated from FPG and fasting C-peptide concentrations. However, as HOMA-B is calculated from fasting values only, and the response over time after a glucose load, it has limited ability to detect chronic β-cell dysfunction, but HOMA is feasible in large studies and has been validated in pregnancy (27). In addition, method-related differences in measurement of 25(OH)D are widespread,

although results from the Hormone laboratory was found reliable compared with the gold standard of measuring 25(OH)D (standardized liquid chromatography-tandem mass spectrometry) (28). Another limitation is that the categorization of 25(OH)D may not be optimal as we do not separate women with a large increase in 25(OH)D from those with only a small increase from just below to above 37 nmol/L.

First, comparing studies may be hampered by different criteria of GDM, different definitions of vitamin D deficiency and methods of 25(OH)D measurements and some studies have very low prevalence of vitamin D among the women included (7, 8). We identified no other study exploring 25(OH)D at several time points during pregnancy in relation to GDM. In contrast to our population-based cohort study, several other observational studies have found an association between 25(OH)D and GDM (7, 8). These studies are for the most either cross-sectional or case-control/nested case-control studies, some are small, and may represent selected groups. Another important issue in observational studies is adjustment for confounders. While most studies adjusted for age, BMI, and some for season of blood drawn, some studies did not adjust for any confounders (10, 11). In line with our study, some other studies did not find an association after adjusting for confounders (7, 8).

An association between vitamin D and body fat have been found in several studies (29, 30). As body fat and weight gain are risk factors for GDM (18, 31), it is important to adjust for body fat as a confounder of the association between vitamin D and GDM. Asians are known to have a body composition with more visceral and central fat, and more fat per BMI unit compared with Western subjects which contributes to an increased insulin resistance, particularly seen in South Asians (32). Therefore, BMI is not a good measure of body fat across populations. Many of the studies have adjusted for BMI or pre-pregnant BMI, although

BMI is affected by physiological changes during pregnancy, with increased body fluid, and weight of the foetus and placenta. In our study in a pregnant population, we measured sum of skinfolds in addition to BMI, in early pregnancy and at time of GDM diagnosis. In our primary analyses, we adjusted for sum of skinfolds and change in sum of skinfolds accounting for increasing fat deposits from inclusion to 28 GW by including change in sum of skinfolds (8). We identified only two studies adjusting for weight gain or other measures of increasing fat deposits during pregnancy (33, 34). In the sensitivity analysis, adjusting for pre-pregnant BMI and weight gain, vitamin D deficiency and GDM was still significantly associated. However, when adjusting for a more direct measure of fat deposits, the association was attenuated and no longer significant, probably reflecting that sum of skinfolds is a better measure of fat deposits in multi-ethnic pregnant populations. Furthermore, of studies that found an association, only few studies adjusted for socioeconomic status and demographic such as ethnicity. Many of these are studies from the USA primarily representing groups with American-African and Hispanic ethnicity in addition to European origin populations (7). Studies from other countries representing other populations provide divergent results as one study from Iran (35) and one study from China (36) found an association, while a study from India did not (37).

Studies exploring relations between 25(OH)D and other measures of glucose metabolism are fewer, results are inconsistent and studies are often hampered with methodological flaws, as few used a longitudinal design and adjustment for confounding factors. Many studies report only correlations, primarily with FPG, insulin and different measures of HOMA, most showing inversely correlations with 25(OH)D. In studies adjusting for confounders, results are inconsistent (33, 35, 38-41).

The most striking finding in our study was that the association with 25(OH)D disappeared after adjusting for ethnicity both for the primary and secondary outcomes. We can only speculate about the reason for this. Ethnicity obviously reflects numerous factors; some may be related to vitamin D and some to GDM, but not necessarily to both. For example, skin pigmentation and use of concealing clothes and minimal sun exposure of the skin are associated with some ethnic groups and vitamin D status, but not necessarily with GDM, although these factors may be related to low levels of physical activity. Life style factors, such as a low fibre - high simple carbohydrate diet and a low physical activity level are strongly related to ethnicity and GDM, but not necessarily vitamin D. We have also found a strong relation with early life factors and GDM explaining some of the excess susceptibility for GDM in ethnic minority groups (42), but the relation with these factors and 25(OH)D is less clear. Further, genes involved in vitamin D metabolism or GDM, but probably not the same genes, could be differentially expressed depending on ethnic origin. Hence, ethnicity is an important confounder, but the effects on the exposure and the outcome are probably mediated through different mechanisms, and could represent cultural, social, genetic or other unmeasured factors.

Generally, most of the observational studies seem to be hampered by poor methodological design and probably residual confounding. Two reviews of trials concluded that vitamin D supplementation did not influence the incidence of GDM, but few and very small trials were found (43, 44). Well-designed randomized controlled trials in multi-ethnic populations with low vitamin D status and high risk of GDM are considered necessary to determine the effect of vitamin D supplementation on prevention of GDM.

Conclusion

Vitamin D deficiency was not associated with GDM or glucose metabolism in a multi-ethnic population-based study, after adjustments for confounding factors. Our findings indicate that confounding by fat deposits and ethnicity explained most of the observed associations in unadjusted analysis.

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Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Table 1. 25-hydroxyvitamin D [25(OH)D] status and confounding variables in the total sample and stratified by gestational diabetes mellitus (GDM) status, WHO 2013 criteria. Values are mean (95% confidence interval) or [numbers (%)]

		GDM (WHO_{2013})		
		Yes	No	p
	n=745	n=235	n=510	
Status at inclusion (15 GW[i])				
Overal mean 25(OH)D (nmol/L)	50.2 (48.3, 52.1)	47.7 (44.0, 51.3)	51.4 (49.2, 53.7)	0.07
25(OH)D <50 nmol/L [n (%)]	389 (52)	141 (60)	248 (49)	**0.01**
25(OH)D status during pregnancy[a]				
Consistently sufficient [n (%)]	417 (57)	109 (47)	308 (61)	**<0.01**
Decreasing [n (%)]	63 (8.6)	22 (9.6)	41 (8.1)	0.50
Increasing [n (%)]	145 (20)	55 (24)	90 (18)	0.06
Consistently deficient [n (%)]	111 (15)	44 (19)	67 (13)	**0.03**
Pre-pregnancy maternal status				
Age (years)	29.8 (29.5, 30.2)	30.3 (29.6, 30.9)	29.6 (29.2, 30.1)	0.12
Ethnicity [n (%)]				
Europe	346 (46.4)	82 (35)	264 (52)	**<0.01**
South Asia	191 (25.6)	81 (35)	110 (22)	**<0.01**
Middle East and North Africa	115 (15.4)	41 (17)	74 (15)	0.49
Sub-Saharan Africa	53 (7.1)	20 (8.5)	33 (6.5)	0.32
East Asia	40 (5.4)	11 (4.7)	29 (5.7)	0.57
Parity [n (%)]				
Para 0	340 (46)	104 (44)	236 (46)	0.61
Para 1	256 (34)	73 (31)	183 (36)	0.18
Para ≥2	149 (20)	58 (25)	91 (18)	**0.03**
Education (years) [n (%)][a]				
<10	122 (16)	50 (21)	72 (14)	**0.02**
10-12	293 (40)	100 (43)	193 (38)	0.20
>12	324 (44)	84 (36)	240 (48)	**<0.01**
Pre-pregnancy BMI[i] (kg/m^2)[a]	24.5 (24.2, 24.9)	25.9 (25.2, 26.6)	23.9 (23.5, 24.3)	**<0.01**
Status at inclusion				
Gestational week	15.1 (14.9, 15.4)	15.2 (14.7, 15.6)	15.1 (14.8, 15.4)	0.74
Sum of skinfolds (mm)[b]	72.0 (70.6, 73.5)	77.0 (74.3, 79.8)	69.8 (68.1, 71.5)	**<0.01**
Season for 25(OH)D measurement [n (%)]				
Summer	347 (47)	130 (55)	217 (43)	**<0.01**
Winter	398 (53)	105 (45)	293 (57)	**<0.01**
Status at 28 GW				
Gestational week[c]	28.3 (28.2, 28.4)	28.2 (28.0, 28.3)	28.3 (28.2, 28.4)	0.20
Δ Sum of skinfolds (15 to 28 GW) (mm)[d]	5.8 (4.8, 6.8)	6.2 (4.5, 7.9)	5.6 (4.3, 6.8)	0.58
Weight gain[ii] (pre-pregnant to 28 GW) (kg)	8.7 (8.3, 9.0)	8.8 (8.1, 9.4)	8.6 (8.2, 9.0)	0.71
Dietary clusters [n (%)][a]				
Healthy	239 (33)	54 (23)	185 (37)	**<0.01**
Unhealthy	493 (67)	179 (77)	314 (63)	**<0.01**

[i]GW: gestational week derived from the 1st day of the woman's last menstrual period,

[ii]BMI: body mass index

Consistently sufficient: 25(OH)D ≥37 nmol/L at 15 and 28 GW

Decreasing: 25(OH)D ≥37 nmol/L at 15 GW and <37 nmol/L at 28 GW

Increasing: 25(OH)D <37 nmol/L at 15 GW and ≥37 nmol/L at 28 GW

Consistently deficient: 25(OH)D <37 nmol/L at 15 and 28 GW

[a]missing information of 5-13 women; [b]n=681; [c]missing information of 1-4 women; [d]n=649

P-values for the differences between GDM and non-GDM. Bold numbers indicate P-values <0.05.

Independent t-test or two-sample test of proportions.

Table 2.

Univariate and multiple regressions between 25-hydroxyvitamin D [25(OH)D] and gestational diabetes mellitus (GDM)[a] (odds ratios and 95% confidence intervals). Associations according to vitamin D deficiency at inclusion (25(OH)D <50 nmol/L) and vitamin D status during pregnancy (consistently sufficient or deficient, increasing or decreasing).

	Univariate analysis				Multiple analysis (Model 1)			Multiple analysis (Model 2)			Multiple analysis (Model 3)		
	n	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
					n=739, R^2=0.064			n=645, R^2=0.113			n=645, R^2=0.130		
25(OH)D sufficiency (≥50 nmol/L) at inclusion (15 GW) (ref)	745												
25(OH)D < 50 nmol/L		1.6	(1.2, 2.2)	**<0.01**	1.6	(1.1, 2.2)	**<0.01**	1.4	(0.95, 2.0)	0.09	1.1	(0.69, 1.6)	0.79
					n=730, R^2=0.065			n=640, R^2=0.108			n=640, R^2=0.127		
25(OH)D Consistently sufficient (ref)	736												
Decreasing		1.5	(0.86, 2.7)	0.15	1.4	(0.77, 2.5)	0.29	1.3	(0.68, 2.4)	0.49	1.1	(0.60, 2.1)	0.69
Increasing		1.7	(1.2, 2.6)	**<0.01**	1.8	(1.2, 2.7)	**<0.01**	1.4	(0.87, 2.2)	0.18	1.0	(0.60, 1.7)	0.97
Consistently deficient		1.9	(1.2, 2.9)	**<0.01**	1.7	(1.0, 2.7)	**0.04**	1.3	(0.74, 2.2)	0.39	0.88	(0.49, 1.6)	0.68

[a]Logistic regression analysis with GDM as dependent variable.

ref: referent value; GW: gestational week; R^2: coefficient of determination.

Model 1: adjusted for age, parity, education, season

Model 2: as model 1, with additional adjustment for sum of skinfolds at visit 1 and change in skinfolds from visit 1 to visit 2

Model 3: as model 2, with additional adjustment for ethnicity/geographic origin

Consistently sufficient: 25(OH)D ≥37 nmol/L at 15 and 28 GW

Decreasing: 25(OH)D ≥37 nmol/L at 15 GW and <37 nmol/L at 28 GW

Increasing: 25(OH)D <37 nmol/L at 15 GW and ≥37 nmol/L at 28 GW

Consistently deficient: 25(OH)D <37 nmol/L at 15 and 28 GW

Table 3.

Separate generalized linear models between 25-hydroxyvitamin D [25(OH)D] and each of the following dependend variables: fasting plasma glucose (FPG), HOMA-IR, fasting insulin and C-peptide (regression coefficients and 95% conficence intervals). Associations according to vitamin D deficiency at inclusion (25(OH)D <50 nmol/L) with vitamin D sufficiency (25(OH)D ≥50 nmol/L) as reference.

	Univariate analysis				Multiple analysis (Model 1)			Multiple analysis (Model 2)			Multiple analysis (Model 3)[a]		
	n	B	(95% CI)	P	B	(95% CI)	P	B	(95% CI)	P	B	(95% CI)	P
FPG[a]:	745	0.13	(0.04, 0.21)	**<0.01**	0.13	(0.04, 0.22)	**<0.01**	0.10	(0.01, 0.20)	**0.04**	0.017	(-0.10, 0.13)	0.77
HOMA-IR[b]:	731	0.16	(0.04, 0.28)	**<0.01**	0.19	(0.07, 0.32)	**<0.01**	0.14	(0.01, 0.27)	**0.03**	0.045	(-0.10, 0.20)	0.54
Insulin[c] **(fasting)**:	731	16	(6.4, 25)	**<0.01**	15.2	(5.6, 25)	**<0.01**	10	(0.39, 20)	**0.04**	-0.13	(-11, 11)	0.98
C-peptide[d] **(fasting)**:	731	70	(14, 125)	**0.01**	84	(26, 141)	**<0.01**	63	(5.2, 122)	**0.03**	21	(-45, 87)	0.54

ref: referent value; GW: gestational week; AIC: Akaike's information criterion.

Model 1: adjusted for age, parity, education, season

Model 2: as model 1, with additional adjustment for sum of skinfolds at visit 1 and change in skinfolds from visit 1 to visit 2

Model 3: as model 2, with additional adjustment for ethnicity/geographic origin

[a]FPG: n=645, AIC=1182; [b]HOMA-IR: n=635, AIC=1482; [c]Insulin: n=635, AIC=6971; [d]C-peptide: n=635, AIC=9259.

Figure 1a. Ethnic variation in gestational diabetes (GDM).

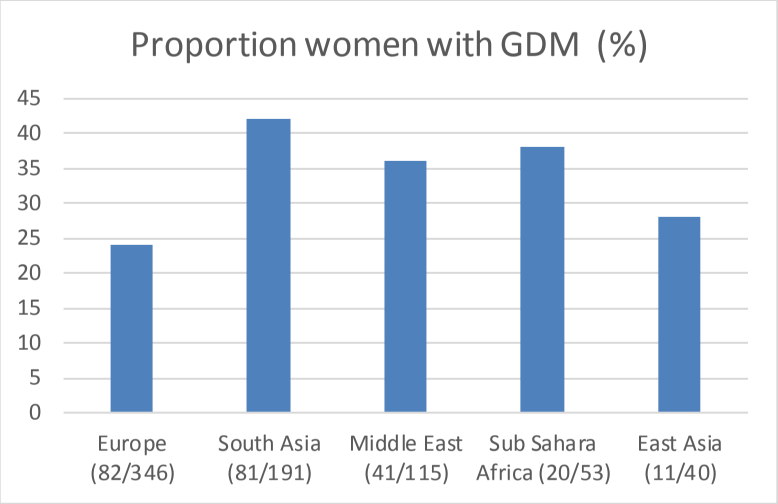
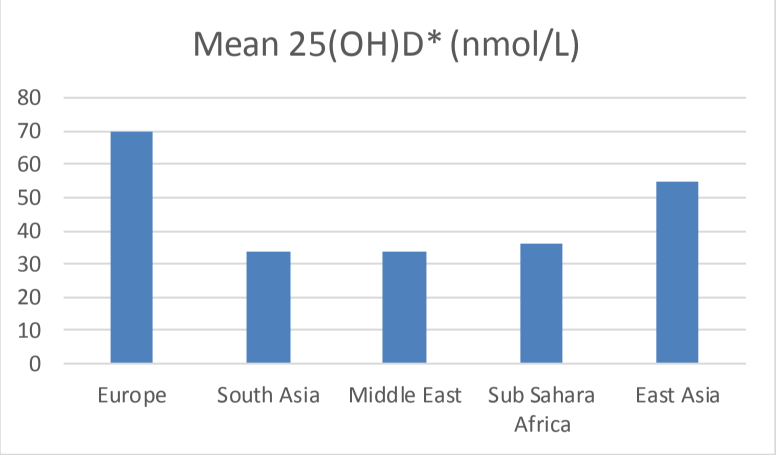
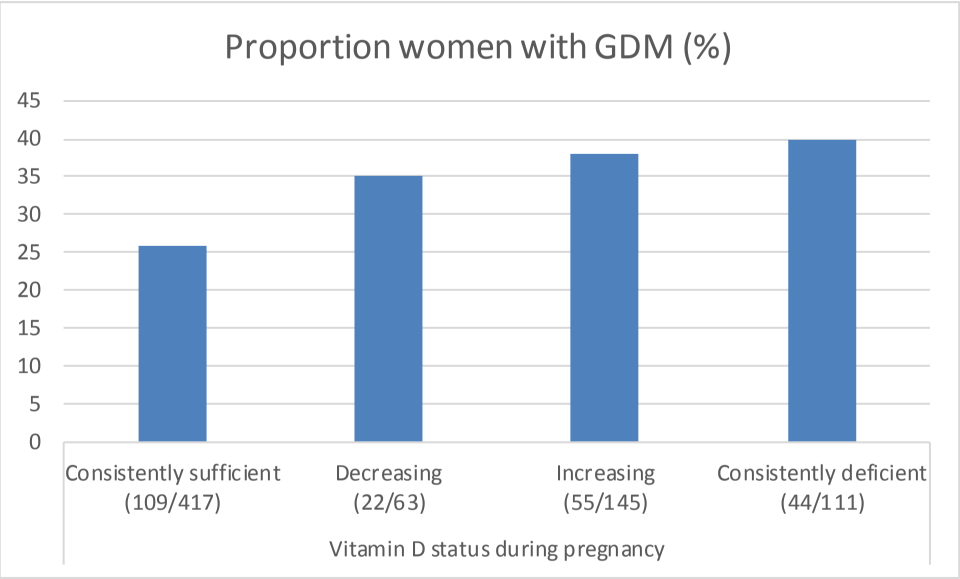


Figure 1b. Ethnic variation in serum 25(OH)D concentrations.



25(OH)D: 25-hydroxyvitamin D, *15 gestational week

Figure 2.



Consistently sufficient: 25(OH)D ≥37 nmol/L at 15 and 28 gestational week (GW)

Decreasing: 25(OH)D ≥37 nmol/L at GW 15 and <37 nmol/L at 28 GW

Increasing: 25(OH)D <37 nmol/L at GW 15 and ≥37 nmol/L at 28 GW

Consistently deficient: 25(OH)D <37 nmol/L at 15 and 28 GW

Supplementary Table 1. Characteristics of the cohort by geographic origin. Values are mean (standard deviation), numbers (%) or median (interquartile range (IQR)).

	Total		Europe		South Asia		Middle East and North Africa		Sub-Saharan Africa		East Asia	
	n=745 (100)		n=346 (46)		n=191 (26)		n=115 (15)		n=53 (7)		n=40 (5)	
	n		n		n		n		n		n	
Pre-pregnancy maternal status												
Age (years)	745	29.8 (4.8)	346	30.7 (4.5)	191	28.7 (4.5)	115	29.6 (5.5)	53	28.2 (5.3)	40	31.5 (4.5)
Parity [n (%)]												
Para 0	340	(45.6)	182	(52.6)	79	(41.4)	40	(34.8)	22	(41.5)	17	(42.5)
Para 1	256	(34.4)	126	(36.4)	64	(33.5)	39	(33.9)	11	(20.8)	16	(40.0)
Para ≥2	149	(20.0)	38	(11.0)	48	(25.1)	36	(31.3)	20	(37.7)	7	(17.5)
Education (years) [n (%)]												
<10	122	(16.5)	15	(4.4)	33	(17.4)	42	(37.2)	24	(45.3)	8	(20.0)
10-12	293	(39.6)	107	(31.2)	96	(50.5)	52	(46.0)	22	(41.5)	16	(40.0)
>12	324	(43.8)	221	(64.4)	61	(32.1)	19	16.8)	7	(13.2)	16	(40.0)
Body height (cm)	745	163.5 (6.6)	346	167.1 (5.6)	191	160.1 (5.7)	115	161.1 (5.4)	53	162.9 (6.0)	40	156.9 (6.3)
Pre-pregnancy body weight (kg)	734	65.7 (14.0)	341	68.5 (13.7)	187	60.8 (11.5)	114	67.3 (14.2)	52	70.0 (17.6)	40	54.9 (9.5)
Pre-pregnancy BMI (kg/m^2)	734	24.5 (4.8)	341	24.5 (4.8)	187	23.7 (4.1)	114	25.9 (5.1)	52	26.2 (6.0)	40	22.2 (3.4)
Previous GDM[a] [n (%)]	21	(5.2)	4	(2.4)	9	(8.0)	6	(8.0)	1	(3.2)	1	(4.3)
Status at inclusion												
Gestational week	745	15.1 (3.4)	346	14.2 (2.4)	191	15.7 (3.9)	115	15.1 (3.4)	53	17.7 (5.0)	40	16.4 (4.0)
25(OH)D (nmol/L)	745	50.2 (26.7)	346	67.1 (23.6)	191	32.4 (18.7)	115	34.2 (19.9)	53	38.1 (17.7)	40	51.4 (17.4)
25(OH)D <50 nmol/L [n (%)]	384	(52.0)	81	(23.5)	159	(84.1)	89	(78.8)	38	(74.5)	17	(42.5)
25(OH)D <37 nmol/L [n (%)]	257	(34.8)	27	(7.8)	125	(66.1)	72	(63.7)	25	(49.0)	8	(20.0)
25(OH)D <25 nmol/L [n (%)]	149	(20.2)	5	(1.4)	85	(45.0)	45	(39.8)	13	(25.5)	1	(2.5)
Body weight (kg)	745	67.7 (14.2)	346	70.3 (13.6)	191	62.5 (11.5)	115	70.0 (15.1)	53	72.5 (17.5)	40	56.7 (10.6)
BMI[b] (kg/m^2)	745	25.3 (4.8)	346	25.2 (4.7)	191	24.4 (4.1)	115	26.9 (5.4)	53	27.3 (6.1)	40	23.0 (3.6)
Weight gain (pre-pregnancy to 15 GW)	734	2.1 (3.7)	341	2.0 (3.3)	187	1.7 (3.6)	114	2.7 (3.9)	52	3.0 (4.9)	40	1.8 (4.1)
Sum of skinfolds (mm)	681	72.0 (19.8)	320	69.5 (19.6)	173	74.3 (18.6)	104	73.9 (19.8)	46	81.8 (21.8)	38	66.2 (18.0)
Status at 28 gestational week												
Gestational week	744	28.3 (1.3)	346	28.2 (1.3)	191	28.2 (1.3)	115	28.4 (1.5)	52	28.4 (1.3)	40	28.2 (1.1)
25(OH)D (nmol/L)	738	58.6 (28.7)	345	70.8 (27.9)	189	45.8 (22.6)	113	51.0 (29.5)	51	45.4 (24.9)	40	52.6 (19.4)
25(OH)D <50 nmol/L [n (%)]	326	(44.2)	90	(26.1)	119	(63.0)	65	(57.5)	32	(62.7)	20	(50.0)
25(OH)D <37 nmol/L [n (%)]	175	(23.7)	28	(8.1)	75	(39.7)	40	(35.4)	22	(43.1)	10	(25.0)
25(OH)D <25 nmol/L [n (%)]	66	(8.9)	5	(1.4)	33	(17.5)	17	(15.0)	10	(19.6)	1	(2.5)
Weight gain (15 to 28 GW)	741	6.6 (3.1)	344	7.0 (2.8)	191	6.5 (3.3)	114	6.8 (3.6)	52	4.6 (3.0)	40	6.2 (2.5)
Weight gain (pre-pregnancy to 28 GW)	731	8.7 (4.7)	339	8.9 (4.6)	187	8.2 (4.6)	114	9.5 (4.9)	51	7.5 (5.3)	40	8.0 (4.3)
Sum of skinfolds (mm)	697	77.5 (18.5)	323	74.2 (18.4)	180	81.5 (18.0)	109	79.1 (18.7)	46	81.5 (19.0)	39	77.2 (16.4)
Change in Sum of skinfolds (mm)	649	5.8 (13.0)	303	5.3 (12.6)	167	7.5 (11.8)	101	4.7 (15.7)	40	-0.3 (10.3)	38	11.0 (13.4)
Dietary clusters [n (%)]												
Healthy	239	(32.7)	194	(56.9)	17	(8.9)	9	(8.0)	9	(18.4)	10	(25.0)
Unhealthy	493	(67.3)	147	(43.1)	173	(91.1)	103	(92.0)	40	(81.6)	30	(25.0)
GDM (WHO 2013 criteria) [n (%)]	235	(31.5)	82	(23.7)	81	(42.4)	41	(35.7)	20	(37.7)	11	(27.5)
GDM (WHO 1999 criteria) [n (%)]	96	(12.9)	39	(11.3)	28	(14.7)	19	(16.5)	4	(7.5)	6	(15.0)
FPG (mmol/L)	745	4.8 (0.6)	346	4.7 (0.6)	191	5.0 (0.6)	115	4.9 (0.7)	53	4.8 (0.6)	40	4.8 (0.6)
2-hour PG (mmol/L)	735	6.2 (1.5)	344	6.0 (1.4)	188	6.4 (1.5)	111	6.3 (1.6)	53	6.3 (1.3)	39	6.6 (1.4)
HOMA-IR[c]*	731	1.6 (1.2-2.1)	340	1.5 (1.2-1.9)	187	1.8 (1.5-2.3)	114	1.6 (1.2-2.3)	50	1.5 (1.0-1.8)	40	1.5 (1.1-1.8)
HOMA-B[d]*	731	173.3 (149.6-199.9)	340	173.5 (149.6-199.7)	187	178.7 (155.3-208.8)	114	169.0 (147.0-200.6)	50	164.9 (140.9-191.0)	40	169.7 (145.6-190.1)
Insulin (pmol/L)*	731	57.0 (38.0-81.0)	340	48.0 (33.0-70.0)	187	74.0 (55.0-97.0)	114	60.0 (41.0-85.3)	50	58.5 (41.0-88.5)	40	52.0 (38.071.3)
C-peptide (nmol/L)*	731	756.0 (576.0-972.0)	340	713.5 (558.8-891.0)	187	860.0 (688.0-1080.0)	114	756.0 (584.3-1052.5)	50	672.0 (495.5-835.0)	40	715.5 (542.3-877.0)
25(OH)D status in categories at both visits [n (%)]												
Consistently sufficient	417	(57)	293	(85)	48	(25)	32	(28)	19	(38)	25	(63)
Decreasing	63	(8.6)	24	(7)	16	(8.5)	9	(8)	7	(14)	7	(18)
Increasing	145	(20)	23	(6.7)	66	(35)	41	(36)	10	(20)	5	(13)
Consistently deficient	111	(15)	4	(1.2)	59	(31)	31	(27)	14	(28)	3	(7.5)

GW: gestational week. Gestational week derived from the 1st day of the woman's last menstrual period.

[a]GDM: gestational diabetes mellitus. WHO (2013 criteria): fasting plasma glucose (FPG) ≥5.1 mmol/L or 2-hour plasma glucose (PG) ≥8.5 mmol/L.

[b]BMI: body mass index

[c]HOMA-IR: Homeostatic Model of Insulin Resistance

[d]HOMA-B: β-cell function

*Median with IQR.

Supplementary Table 2.

25-hydroxyvitamin D [25(OH)D] status in the total sample and stratified by gestational diabetes mellitus (GDM) status, WHO 2013 criteria. Values are mean (95% confidence interval) or [numbers (%)].

		GDM (WHO_{2013})		
		Yes	No	p
	n=745	n=235	n=510	
Status at inclusion (15 GW[i])				
Overal mean 25(OH)D (nmol/L)	50.2 (48.3, 52.1)	47.7 (44.0, 51.3)	51.4 (49.2, 53.7)	0.07
25(OH)D <50 nmol/L [n (%)]	389 (52)	141 (60)	248 (49)	**<0.01**
25(OH)D <37 nmol/L [n (%)]	259 (35)	100 (43)	159 (31)	**<0.01**
25(OH)D <25 nmol/L [n (%)]	150 (20)	56 (24)	94 (18)	0.06
Status at 28 GW[i]				
Overal mean 25 (OH)D	58.6 (56.6, 60.7)	57.1 (53.3, 60.9)	59.3 (56.9, 61.8)	0.34
25(OH)D <50 nmol/L [n (%)]	326 (44)	108 (47)	218 (43)	0.34
25(OH)D <37 nmol/L [n (%)]	175 (24)	66 (29)	109 (22)	**0.04**
25(OH)D <25 nmol/L [n (%)]	66 (8.9)	30 (13)	36 (7.1)	**<0.01**

iGW: gestational week derived from the 1st day of the woman's last menstrual period.

P-values for the differences between GDM and non-GDM. Bold numbers indicate P-values <0.05.

Independent t-test or chi-square .

Supplementary Table 3.

Spearman's rank correlation coefficients between 25-hydroxyvitamin D [25(OH)D] at inclusion (15 GW) and measures of glucose metabolism at 28 GW.

		p-value
HOMA-IR[a]	**-0.116**	**0.002**
HOMA-B[b]	-0.006	0.878
FPG[c]	**-0.128**	**0.001**
2-hour PG	-0.056	0.13
Insulin	**-0.212**	**0.000**
C-peptid	**-0.111**	**0.003**

n=697

GW: gestational week

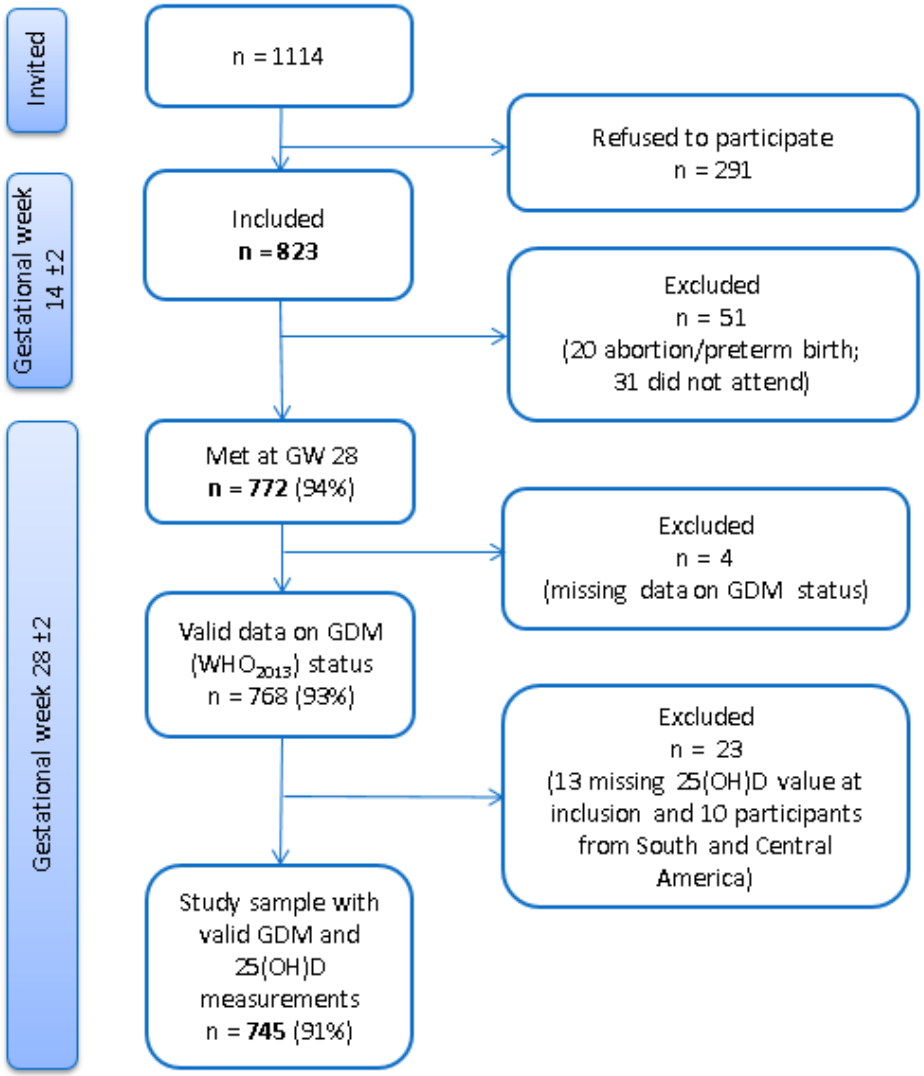
[a]HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

[b]HOMA-B: Homeostatic Model Assessment of β-cell function

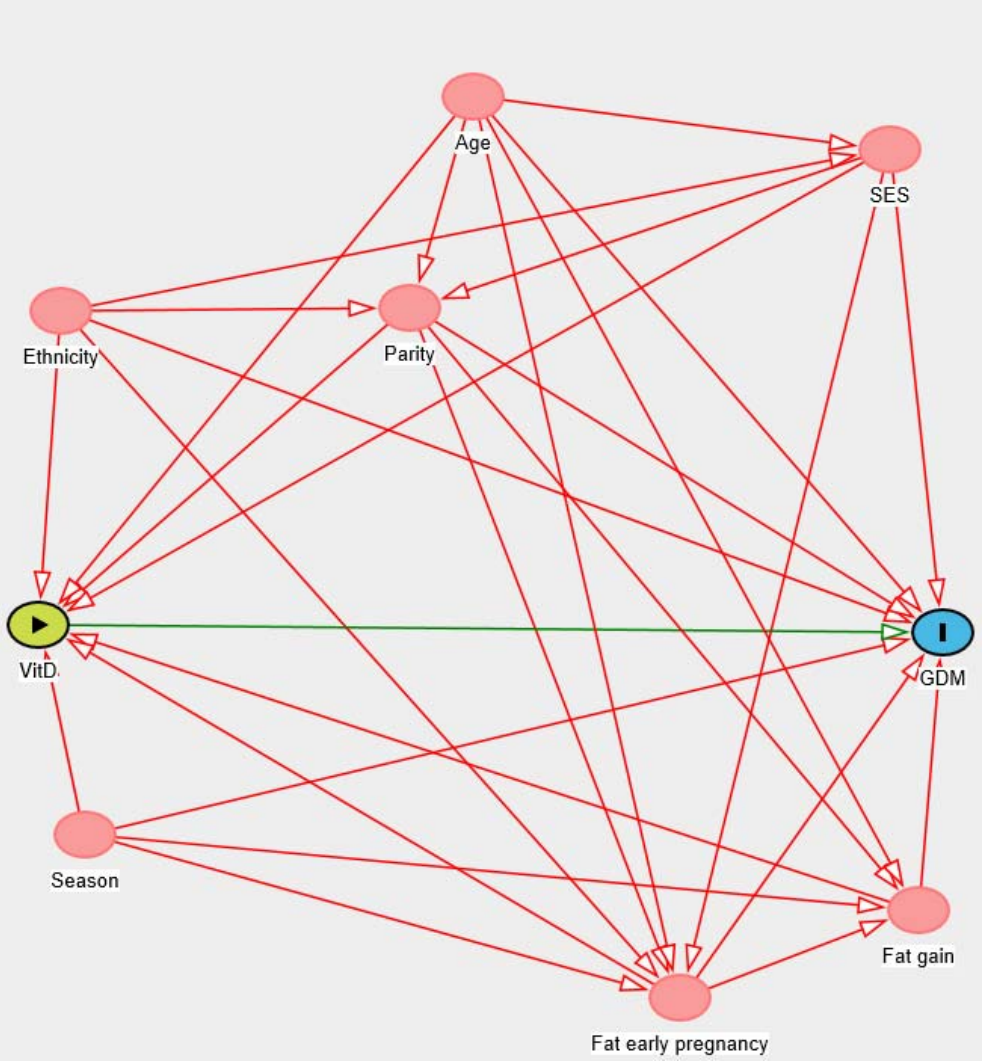
[c]FPG: fasting plasma glucose

Bold numbers indicate P-values <0.05.

Supplementary figure 1.



Supplementary figure 2.



Directed Acyclic Graph of confounders between vitamin D (25(OH)D and gestational diabetes mellitus (GDM).

III

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Vitamin D levels during pregnancy and associations with birth weight and body composition of the newborn: a longitudinal multiethnic population-based study

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Abstract

We investigated associations between serum 25-hydroxyvitamin D (25(OH)D) in pregnancy and birth weight and other neonatal anthropometric measures. The present study was a population-based, multiethnic cohort study of 719 pregnant women (59 % ethnic minorities) in Oslo, Norway, delivering a singleton neonate at term and with birth weight measurements. In a representative sample, anthropometric measurements were taken. Maternal 25(OH)D was measured at gestational weeks 15 and 28. Women with 25(OH)D <37 nmol/l were recommended vitamin D_3 supplementation. Separate linear regression analyses were performed to model the associations between 25(OH)D and each of the outcomes: birth weight, crown–heel length, head circumference, abdominal circumference, sum of skinfolds, mid-upper arm circumference and ponderal index. In early pregnancy, 51 % of the women were vitamin D deficient (25(OH)D < 50 nmol/l). In univariate analyses and in models adjusting for maternal age, parity, education, prepregnancy BMI, season, gestational age and neonate sex, maternal 25(OH)D was significantly associated with birth weight, head circumference, abdominal circumference and ponderal index ($P < 0{\cdot}05$ for all), when used as a continuous variable and categorised (consistently low, consistently high, increasing and decreasing level). However, after adjusting for ethnicity, 25(OH)D was no longer associated with any of the outcomes. Sex-specific associations for abdominal circumference and sum of skinfolds were found ($P_{\text{for interaction}} < 0{\cdot}05$). In conclusion, in a multiethnic cohort of pregnant women with high prevalence of vitamin D deficiency, we found no independent relation between maternal vitamin D levels and any of the neonatal anthropometric measures, and the strong association between ethnicity and neonatal outcomes was not affected by maternal vitamin D status.

Key words: Vitamin D: Deficiencies: Pregnancy: Ethnic minorities: Birth weight: Body composition: Anthropometric measures

Early life environment plays an important role for later susceptibility to chronic diseases. Inverse associations between birth weight and later risk for CVD and type 2 diabetes have been reported in several populations[1–3]. However, subtle variations in environmental influences, such as nutritional factors, can probably produce a range of neonatal phenotypes which may affect the risk for adult disease, even in the absence of effects on birth weight[4].

Birth weight and neonatal body composition vary considerably across the world, and also between ethnic groups living in Europe. Neonates of mothers with origin from Asia and Africa have lower birth weight, smaller abdominal circumference and less fat-free mass, but similar amounts of fat mass, compared with neonates of European origin[5–9]. This phenotype seems to track throughout life and is associated with a higher risk for CVD and type 2 diabetes, as observed in several ethnic minority groups in Europe[10].

Vitamin D is essential for fetal and childhood skeletal development[11], and experimental animal studies support an active contribution of vitamin D to organ development[12,13]. However, the effect of maternal vitamin D deficiency on birth weight and body composition is not clear. Several studies have reported a positive association between maternal vitamin D levels in pregnancy and offspring birth weight[14], although results are inconsistent, both from observational[15–17] and randomised controlled studies (RCT)[15,17–19]. A Cochrane review from 2016, of RCT with vitamin D supplementation *v.* placebo, reported no significant effect on birth weight. Furthermore, although there was some indication that vitamin D supplementation increased infant length and head circumference at birth, the clinical significance of the observed effects of an increased vitamin D level is still unclear[19]. In addition, few studies investigating the effect of vitamin D on neonatal size have included other anthropometric data than birth weight, many of these studies were small or only included women with moderate vitamin D deficiency. Just a few studies included ethnic minority women, with presented results stratified by ethnicity or adjusted for ethnicity[20–23]. This is particularly important, as the prevalence of severe vitamin D deficiency is

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; GW, gestational week; SGA, small for gestational age.

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high among pregnant ethnic minority women compared with ethnic Europeans[24]. Whether low levels of vitamin D can contribute to low birth weight in ethnic minorities have been questioned. An independent association between maternal vitamin D levels and offspring birth weight or body composition would lend support to identifying these women early in pregnancy to offer vitamin D substitution.

Our aim was to explore associations between maternal 25-hydroxyvitamin D (25(OH)D) and neonatal birth weight and a wide range of anthropometric measurements to reflect body composition, before and after adjusting for other potentially explanatory factors, especially ethnicity.

Methods

Design, setting and study population

Data are from a population-based, prospective cohort of 823 presumably healthy women attending Maternal and Child Health Clinics (MCHC) for antenatal care in Groruddalen, Oslo, Norway, between May 2008 and March 2010, and their offspring (The STORK Groruddalen study)[25]. The majority (75–85 %) of pregnant women residing in this area, situated at a latitude of 60°N, attend the Child Health Clinics for antenatal care. Antenatal care is free of charge in Norway and easily accessible. The study design has been described in detail elsewhere[25]. In short, information material and questionnaires were translated to Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu and Vietnamese and quality checked by bilingual health professionals. Women were eligible if they (1) lived in the district, (2) planned to give birth at one of the two study hospitals, (3) were in gestational week (GW) <20, (4) were not suffering from diseases necessitating intensive hospital follow-up during pregnancy, (5) could communicate in Norwegian or any of the specified languages and (6) were able to provide written consent to participate. In total, 59 % of the included women were of an ethnic minority background. The participation rate was 74 % (range: 64–83 % between ethnic groups), and the participating women were considered to be representative of the main ethnic groups attending MCHC[25]. Maternal data were collected at 15 and 28 weeks of gestation, through interviews by study personnel (assisted by professional interpreters when needed). Clinical measurements for mothers and neonates were performed and blood samples collected according to the study protocol.

Variables

Main outcome measures. Outcome variables were birth weight, crown–heel length, head circumference, abdominal circumference, sum of skinfolds, mid-upper arm circumference and ponderal index. Birth weight was routinely measured immediately after delivery by hospital staff. The other outcome variables were measured within 72 h after birth unless there were medical contraindications. Neonatal anthropometric measurements were performed by specially trained study personnel[5]. Skinfold thickness was the sum of the triceps skinfold, the subscapular skinfold, the supra-iliac skinfold and the thigh skinfold, and named 'sum of skinfolds'. All measurements, except length, were performed twice (circumferences and length to the nearest 0·1 cm, skinfolds to the nearest 0·1 mm) and calculated as the mean of two measurements. Ponderal index was calculated as birth weight (kg)/crown–heel length (m^3)[5,25]. Small for gestational age (SGA) was defined as <10th percentile according to the Norwegian national references[26].

Explanatory factors. At GW 15 and 28, maternal 25(OH)D was analysed by competitive RIA (DiaSorin) at the Hormone Laboratory, Oslo University Hospital, Aker. The method measures total 25(OH)D (both 25(OH)D_2 and D_3). The interassay CV gives information on the variation between measures in different batches; the lowest CV was 13 % and the highest CV was 16 % between 37 and 131 nmol/l for this method at the laboratory during the period from 2008 to 2010. The laboratory is accredited by the International Organization for Standardization and is part of the Vitamin D Quality Assessment Scheme. Concentrations of 25(OH)D <12 nmol/l were replaced with '11 nmol/l' in the calculations (n 16), so as to not overestimate the effect of low vitamin D status. The laboratory's reference range was 37–131 nmol/l based on the ethnic Norwegian population from the Oslo Health Study[27]. Preplanned, and according to the protocol, women with 25(OH)D less than the laboratory's lower reference range (<37 nmol/l) at GW 15 and 28 were provided written information about their 25(OH)D concentration, and recommended to consult their general practitioner for treatment[24].

Maternal and offspring ethnic origin was defined by the pregnant participant's mother's country of birth[28]. Ethnicity was further categorised into European (primarily from Norway and Sweden), Asian (primarily from Pakistan, Sri Lanka, Vietnam, India and the Philippines) and Middle Eastern/North African including the Horn of Africa (primarily from Somalia, Iraq, Turkey, Morocco and Afghanistan) (see footnote in Table 1). Parity was categorised as no (nulliparous), one (uniparous) or two or more (multiparous) previous pregnancies lasting >22 weeks. Education level was categorised as <10, 10–12 (high school education) and >12 (college/university education) years. Season of birth was categorised as summer (June, July, August), autumn (September, October, November), winter (December, January, February) and spring (March, April, May). Prepregnancy BMI (calculated from self-reported weight before pregnancy and height measured at inclusion), maternal age, GW at birth (derived from the 1st day of the woman's last menstrual period and neonate sex were other variables of interest.

Ethics

The Regional Committee for Medical and Health Research Ethics for South-Eastern Norway (Ref. 2007/894) and the Norwegian Data Inspectorate approved the study protocol. Participation was based on informed written consent.

Statistical methods

Descriptive statistics are presented as frequencies, mean values and standard deviations and proportions. All continuous

response variables were assessed for normality. Separate generalised linear models were performed to assess the relationship between the concentration of 25(OH)D and each of the following outcomes: birth weight, crown–heel length, head circumference, abdominal circumference, sum of skinfolds, mid-upper arm circumference and ponderal index. The study sample including preterm singleton (<37 weeks) neonates were used when analysing associations with SGA as the outcome (see flow chart, online Supplementary Fig. S1), and generalised logistic regression models were performed to assess the relationship between 25(OH)D and SGA. We accounted for the following potential explanatory factors: GW, neonate sex, season, maternal age, parity, education, prepregnancy BMI and ethnicity. Maternal 25(OH)D was first analysed as a continuous variable. We also categorised the 25(OH)D level during pregnancy as: *consistently sufficient level* (≥37nmol/l at GW 15 and 28), *consistently deficient level* (<37 nmol/l at GW 15 and 28), *increasing level* (<37 nmol/l at GW 15 and ≥37 nmol/l at GW 28) and *decreasing* level (≥37nmol/l at GW 15 and <37 nmol/l at GW 28). Variables with $P<0{\cdot}2$ in the univariate analyses were included in the multiple regression analyses. Interactions between 25(OH)D and sex, between 25(OH)D and ethnicity and between ethnicity and season, were examined graphically and by adding interaction terms into the models. Results are presented as linear regression coefficients (β) and OR and 95 % CI. $P<0{\cdot}05$ were considered statistically significant. Given the sample size, the actual CI are very small for the outcomes and thereby these results indicate precise estimates. SPSS software (version 22; IBM SPSS Statistics) and StataSE 14 were used for statistical analysis.

Results

Study sample

Of the 823 women included in the STORK Groruddalen project, twelve women from South or Central America and seventeen women from African countries other than North Africa including the Horn of Africa with low numbers of participating women were excluded because of low sample size. We also excluded thirty-six women with a multiple pregnancy, an abortion, a stillbirth, a neonatal death or with missing data at birth, leaving 758 (92 %) available for analyses of the outcome SGA. After excluding thirty-nine women with premature deliveries (<37 weeks), the main study sample consisted of 719 (87 %) live-born term neonates (flow chart, online Supplementary Fig. S1). Anthropometric data were obtained from 517 to 690 of these newborns.

Maternal 25-hydroxyvitamin D status. In early pregnancy, 51 % of the women had vitamin D deficiency, defined as 25(OH)D <50 nmol/l, ranging from 78 % among Middle Eastern/North African, 76 % among Asian and 24 % among European women. A high prevalence of severe deficiency (25(OH)D <25 nmol/l) was found among women from Asia (36 %) and the Middle East (36 %) compared with 1·7 % among Europeans. At inclusion, the mean 25(OH)D concentration values ranged from 35 to 67 nmol/l between the ethnic groups. However, ethnic differences were reduced at GW 28 after recommending vitamin D supplementation (Table 1). Maternal and infant characteristics related to 25(OH)D are presented in online Supplementary Table S1.

Association between maternal 25-hydroxyvitamin D and birth weight. The mean birth weight was 3485 (SD 501) g, but differed by ethnic groups ($P<0{\cdot}01$ for all): 3623 g among European, 3455 g among Middle Eastern and 3286 g among Asian neonates (Table 1 and online Supplementary Table S1). Maternal 25(OH)D at inclusion was positively associated with birth weight in univariate analysis, and also after adjusting for maternal age, parity, educational level, prepregnancy BMI, season, gestational age and neonate sex ($P<0{\cdot}01$) (model 1, Table 2). However, after additional adjustment for ethnicity, 25(OH)D was no longer associated with birth weight (model 2, Table 2). Similar results were found for the association between 25(OH)D at GW 28 and birth weight (online Supplementary Table S3). This was also the case when using the categorised variable which reflected the 25(OH)D level throughout pregnancy (Table 3). Before adjusting for ethnicity, the mean birth weight was lower in neonates of women with consistently deficient (–116 g), or initially low, but increasing 25(OH)D (–105 g) compared with neonates of women with consistently sufficient 25(OH)D (reference) (model 1, Table 3). However, after additional adjustment for ethnicity, 25(OH)D levels during pregnancy were no longer associated with birth weight (compared with the reference group, neonates with consistently deficient mothers had 2·6 g higher birth weight and neonates with mothers having increasing 25(OH)D had 4·8 g lower birth weight (model 2, Table 3)). Similar results, where the association with 25(OH)D was not present after inclusion of ethnicity, were found from the logistic regression model of SGA as outcome (Table 4). Asian and Middle Eastern ethnic origins were associated with lower birth weight, independently of maternal 25(OH)D levels (not shown). Other factors independently associated with birth weight in the final model were parity, maternal BMI, offspring sex and duration of gestation.

Associations between maternal 25-hydroxyvitamin D and other neonatal anthropometric measures. Maternal 25(OH)D at inclusion was associated with crown–heel length, head circumference, abdominal circumference and ponderal index in univariate analyses and in models adjusted for maternal age, parity, educational level, prepregnancy BMI, season, gestational age and neonate sex. However, none of these outcomes was associated with maternal 25(OH)D when ethnicity was included in the models (Table 2). Results were similar when using levels of 25(OH)D during pregnancy (categories) or in GW 28 (Table 3 and online Supplementary Table S3). Asian origin was associated with lower crown–heel length, head circumference, abdominal circumference, sum of skinfold and ponderal index, and this association was not influenced by maternal 25(OH)D levels (not shown).

Interactions between neonate sex and 25-hydroxyvitamin D. We also tested for effect modifications, and we found no significant interactions or non-significant trends indicating that the effect of 25(OH)D on neonatal anthropometry differed by ethnicity (data not shown). However, we found a significant

Table 1. Maternal and infant characteristics stratified by geographic origin*
(Mean values and standard deviations; numbers and percentages)

	Total (*n* 719) 100 %		Europe (*n* 346)† 48 %		Asia (*n* 216) 30 %		Middle East and North Africa (*n* 157)‡ 22 %	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Maternal characteristics								
Prepregnancy maternal status								
Age (years)	29·8	4·8	30·5	4·4	29·1	4·6	29·1	5·4
Parity								
Parity 0								
n	324		183		87		54	
%	45		53		40		34	
Parity 1								
n	252		126		78		48	
%	35		36		36		31	
Parity ≥2								
n	143		37		51		55	
%	20		11		24		35	
Education level (years)§								
<10								
n	121		15		40		66	
%	17		4·4		19		43	
10–12								
n	280		110		104		66	
%	39		32		48		43	
>12								
n	312		218		71		23	
%	44		64		33		14	
Prepregnancy BMI (kg/m^2)§	24·5	4·8	24·5	4·8	23·4	4·0	25·9	5·5
Status at inclusion (gestational week 15)‖								
Gestational week	15·4	3·5	14·7	2·5	16·0	4·1	16·2	4·1
25(OH)D (nmol/l)	50	27	67	24	36	20	35	19
25(OH)D <50 nmol/l								
n	369		82		165		122	
%	51		24		76		78	
25(OH)D <37 nmol/l								
n	205		27		127		96	
%	35		7·8		59		61	
25(OH)D <25 nmol/l								
n	140		6		78		56	
%	20		1·7		36		36	
Status at gestational week 28¶								
Gestational week	28·8	1·4	28·8	1·4	28·8	1·3	29·0	1·6
25(OH)D nmol/l	59	29	71	28	47	22	48	28
25(OH)D <50 nmol/l								
n	300		85		124		91	
%	42		25		57		58	
25(OH)D <37 nmol/l								
n	164		27		77		60	
%	23		7·8		36		38	
25(OH)D <25 nmol/l								
n	63		5		32		26	
%	8·8		1·4		15		17	
Neonatal characteristics								
Gestational age at birth (weeks)	40·1	1·3	40·3	1·3	39·9	1·3	40·0	1·5
Neonate sex (boy)								
n	356		180		112		64	
%	49·5		52·0		51·9		40·8	
Birth weight (g)	3485	501	3623	472	3286	469	3455	512
Crown–heel length (cm) (*n* 665)	50·0	2·1	50·3	2·0	49·6	2·0	49·7	2·2
Head circumference (cm) (*n* 690)	34·9	1·4	35·2	1·3	34·5	1·4	34·8	1·5
Abdominal circumference (cm) (*n* 517)	32·0	2·3	32·7	2·1	31·0	2·1	32·0	2·0
Sum of skinfolds (mm) (*n* 518)	18·1	3·9	18·7	4·0	17·1	4·0	18·0	3·4
Mid-upper arm circumference (cm) (*n* 516)	11·4	1·0	11·5	1·0	11·1	1·0	11·4	0·94
Ponderal index (kg/m^3) (*n* 665)	27·9	2·6	28·4	2·5	26·9	2·3	28·1	2·8

25(OH)D, 25-hydroxyvitamin D.
* Countries with ≥10 individuals are listed: 346 women from Europe, primarily from Norway (*n* 278) and Sweden (*n* 11); 216 women from Asia, primarily from Pakistan (*n* 111), Sri Lanka (*n* 55), Vietnam (*n* 16), India (*n* 12) and the Philippines (*n* 10); 157 women from the Middle East/North Africa‡, primarily from Somalia (*n* 35), Iraq (*n* 34), Turkey (*n* 26), Morocco (*n* 23) and Afghanistan (*n* 12).
† Including 3 women from USA and Canada.
‡ Including Horn of Africa.
§ Incomplete data on the variables because of missing values for 6–12 women.
‖ Incomplete data on the variables because of missing values for 14 women.
¶ Incomplete data on the variables because of missing values for 36 women.

Table 2. Associations between 25-hydroxyvitamin D (25(OH)D) (continuous) in early pregnancy and neonatal anthropometric measures (*n* 719)† (Regression coefficients and 95 % confidence intervals)

		Univariate analysis			Multiple analysis (model 1)‡			Multiple analysis (model 2)§‖		
Outcomes	*n*	*B*	95 % CI	*P*	*B*	95 % CI	*P*	*B*	95 % CI	*P*
Birth weight										
25(OH)D at GW 15	705	2·9	1·5, 4·2	<0·01**	2·0	0·7, 3·3	<0·01**	−0·08	−1·6, 1·4	0·92
Crown–heel length										
25(OH)D at GW 15	651	0·007	0·001, 0·013	0·02*	0·001	−0·005, 0·007	0·82	−0·004	−0·01, 0·003	0·24
Head circumference										
25(OH)D at GW 15	677	0·01	0·004, 0·012	<0·01**	0·005	0·002, 0·01	<0·01**	0·002	−0·002, 0·006	0·33
Abdominal circumference										
25(OH)D at GW 15	509	0·02	0·01, 0·03	<0·01**	0·015	0·01, 0·02	<0·01**	0·005	−0·004, 0·01	0·26
Sum of skinfolds										
25(OH)D at GW 15	510	0·01	−0·01, 0·02	0·25	0·002	−0·01, 0·02	0·75	−0·01	−0·03, 0·006	0·22
Mid-upper arm circumference										
25(OH)D at GW 15	508	0·003	0·000, 0·006	0·07	0·002	−0·001, 0·006	0·15	0·000	−0·004, 0·004	0·92
Ponderal index										
25(OH)D at GW 15	651	0·01	0·006, 0·02	<0·01**	0·016	0·01, 0·02	<0·01**	0·007	−0·002, 0·017	0·11

GW, gestational week; AIC, Akaike's information criterion.
* $P<0·05$, ** $P<0·01$.
† Generalised linear regression analysis with birth weight, length, head circumference, abdominal circumference, sum of skinfolds, mid-upper arm circumference and ponderal index (at gestation age >37 weeks) as dependent variables.
‡ Adjusted model 1; multiple regression, additional adjustment for neonate sex, gestational age, season, maternal age, parity, educational level and prepregnancy BMI.
§ Adjusted model 2; as model 1, with additional adjustment for geographic origin.
‖ Birth weight: *n* 693, AIC = 10 376; crown–heel length: *n* 639, AIC = 2608; head circumference: *n* 666, AIC = 2151; abdominal circumference: *n* 502, AIC = 213; sum of skinfolds: *n* 503, AIC = 2768; mid-upper arm circumference: *n* 501, AIC = 1364; ponderal index: *n* 639, AIC = 2970.

interaction between neonate sex and 25(OH)D at GW 15 for abdominal circumference (*P* 0·01) and sum of skinfolds (*P* 0·02). Nevertheless, these interaction terms were not entered into the final models, as they only marginally affected the effect estimates. When we stratified by neonate sex in the adjusted model including ethnicity, we found that for each unit increase in 25(OH)D, the estimated abdominal circumference increased (0·01 cm (*P* 0·04)) in girls but not in boys. Similarly for each unit's increase in 25(OH)D, the estimated sum of skinfolds decreased (0·03 mm (*P* 0·02)) for boys only.

Discussion

Main findings

In our multiethnic population with high prevalence of vitamin D deficiency in early pregnancy, we found strong associations between maternal 25(OH)D and birth weight and measures of neonatal body composition, when adjusted for gestational age, neonate sex, season, maternal age, parity, education and prepregnancy BMI. However, after including ethnicity in the models, maternal 25(OH)D in pregnancy was no longer associated with birth weight or any of the offspring anthropometric measures reflecting body composition at birth, whereas the strong association between ethnicity and the neonatal outcomes persisted. These results were consistent, irrespective of whether 25(OH)D was measured in GW 15 or 28, or whether changes in 25(OH)D levels were observed between these time points. Our results, however, may suggest sex-specific associations for some outcomes like abdominal circumference and sum of skinfolds.

Strengths and limitations

The strengths of the present study include its population-based longitudinal design, the high attendance rate, minor loss to follow-up and the relatively large sample size in a multiethnic European context. The questionnaires in nine different languages, available professional interpreters and data collection methods facilitated inclusion of ethnic minorities, even illiterate women. Not least, we have a representative sample of neonates with standardised detailed neonatal anthropometric measurements[5]. Relevant explanatory factors were included, and 25(OH)D was measured at two time points in pregnancy. Further, in accordance with recent studies[29], we have specifically explored interactions with infant sex. Blood samples were collected and analysed with standardised methods at the same high-quality laboratory, and 25(OH)D levels ranged from highly sufficient to severely deficient, with 51 % < 50 nmol/l. Method-related differences in measurement of 25(OH)D are widespread, and as a consequence the Vitamin D Standardization Program developed protocols for standardising 25(OH)D worldwide; the 'gold standard' of measuring 25(OH)D is standardised liquid chromatography-tandem MS (LC-MS/MS). On reanalysing 25(OH)D data from four Nordic population samples by LC-MS/MS and comparing results from the immunoassay methods with the 'gold standard' method, the results from the Hormone Laboratory, Oslo University Hospital, were found to be only modestly changed, indicating that the analyses were reliable[30].

The main limitation of this study is that we have merged ethnic groups to represent large geographical regions based on country of birth. Consequently, we cannot rule out that differences within the Asian and Middle Eastern groups may exist. Statistical power may also be a limitation. However, CI of the effect estimates for the association between 25(OH)D levels and neonatal size were very small, indicating a relatively precise estimate. Hence, we would need a very large sample size to find significant differences, and the clinical relevance of such small effects, although statistically significant, could be questioned. Furthermore, the categorisation of 25(OH)D may not be optimal as we do not separate women with a

Table 3. Associations between 25-hydroxyvitamin D (25(OH)D) (categorical) during two times in pregnancy and neonatal anthropometric measures (*n* 719)† (Regression coefficients and 95 % confidence intervals)

		Univariate analysis			Multiple analysis (model 1)‡			Multiple analysis (model 2)§‖		
Outcomes	*n*	*B*	95 % CI	*P*	*B*	95 % CI	*P*	*B*	95 % CI	*P*
Birth weight										
Consistently sufficient (Ref)¶	375									
Decreasing††	60	−6·4	−140, 127	0·93	−43	−164, 78	0·49	9·9	−110, 130	0·87
Increasing‡‡	134	−148	−245, −51	<0·01**	−105	−195, −16	0·02*	−4·8	−100, 91	0·92
Consistently deficient§§	103	−180	−287, −73	<0·01**	−116	−218, −14	0·03*	2·6	−108, 113	0·96
Crown–heel length										
Consistently sufficient (Ref)	349									
Decreasing	52	0·08	−0·53, 0·68	0·81	−0·03	−0·58, 0·51	0·90	0·09	−0·47, 0·64	0·76
Increasing	124	−0·36	−0·79, 0·07	0·10	−0·04	−0·43, 0·35	0·84	0·16	−0·27, 0·59	0·46
Consistently deficient	94	−0·29	−0·77, 0·18	0·23	0·02	−0·43, 0·47	0·92	0·27	−0·23, 0·76	0·29
Head circumference										
Consistently sufficient (Ref)	361									
Decreasing	57	−0·05	−0·43, 0·33	0·79	−0·13	−0·48, 0·21	0·46	−0·04	−0·39, 0·31	0·82
Increasing	127	−0·36	−0·63, −0·08	0·01*	−0·21	−0·46, 0·05	0·11	−0·03	−0·31, 0·25	0·82
Consistently deficient	101	−0·49	−0·79, −0·19	<0·01**	−0·26	−0·55, 0·03	0·07	−0·06	−0·38, 0·25	0·70
Abdominal circumference										
Consistently sufficient (Ref)	286									
Decreasing	47	0·14	−0·54, 0·83	0·69	−0·03	−0·70, 0·63	0·92	0·35	−0·31, 1·0	0·30
Increasing	98	−0·90	−1·4, −0·39	<0·01**	−0·83	−1·3, −0·34	<0·01**	−0·21	−0·74, 0·32	0·44
Consistently deficient	67	−0·96	−1·5, −0·37	<0·01**	−0·74	−1·3, −0·15	0·02*	−0·04	−0·60, 0·68	0·91
Sum of skinfolds										
Consistently sufficient (Ref)	286									
Decreasing	48	−0·37	−1·6, 0·84	0·55	−0·43	−1·6, 0·75	0·48	−0·12	−1·3, 1·1	0·85
Increasing	98	−0·39	−1·3, 0·52	0·40	−0·29	−1·2, 0·59	0·52	0·23	−0·76, 1·2	0·65
Consistently deficient	67	−1·2	−2·2, −0·10	0·03*	−1·0	−2·1, 0·07	0·07	−0·36	−1·5, 0·83	0·55
Mid-upper arm circumference										
Consistently sufficient (Ref)	285									
Decreasing	48	0·15	−0·16, 0·46	0·35	0·04	−0·26, 0·33	0·81	0·10	−0·20, 0·40	0·51
Increasing	97	−0·20	−0·43, 0·03	0·10	−0·20	−0·42, 0·03	0·09	−0·08	−0·33, 0·17	0·51
Consistently low	67	−0·22	−0·49, 0·05	0·11	−0·16	−0·43, 0·11	0·25	−0·02	−0·31, 0·28	0·92
Ponderal index										
Consistently sufficient (Ref)	349									
Decreasing	52	−0·18	−0·93, 0·57	0·64	−0·24	−0·98, 0·51	0·53	0·07	−0·68, 0·81	0·86
Increasing	124	−0·61	−1·1, −0·08	0·02*	−0·72	−1·3, −0·18	<0·01**	−0·24	−0·82, 0·33	0·41
Consistently deficient	94	−0·82	−1·4, −0·23	<0·01**	−0·87	−1·5, −0·25	<0·01**	−0·30	−0·97, 0·37	0·38

Ref, referent values; GW, gestational week; AIC, Akaike's information criterion.
* $P < 0{\cdot}05$, ** $P < 0{\cdot}01$.
† Generalised linear regression analysis with birth weight, length, head circumference, abdominal circumference, sum of skinfolds, mid-upper arm circumference and ponderal index (at gestation age > 37 weeks) as dependent variable.
‡ Adjusted model 1; multiple regression, additional adjustment for neonate sex, gestational age, season, maternal age, parity, educational level and prepregnancy BMI.
§ Adjusted model 2; as model 1, with additional adjustment for geographic origin.
‖ Birth weight: *n* 661, AIC = 9898; crown–heel length: *n* 608, AIC = 2479; head circumference: *n* 636, AIC = 2054; abdominal circumference: *n* 491, AIC = 2099; sum of skinfolds: *n* 492, AIC = 2709; mid-upper arm circumference: *n* 490, AIC = 1341; ponderal index: *n* 608, AIC = 2844.
¶ Consistently sufficient: 25(OH)D ≥ 37 nmol/l at GW 15 and 28.
†† Decreasing: 25(OH)D ≥ 37 nmol/l at GW 15 and <37 at GW 28.
‡‡ Increasing: 25(OH)D < 37 nmol/l at GW 15 and ≥37 at GW 28.
§§ Consistently deficient: 25(OH)D < 37 nmol/l at GW 15 and 28.

large increase in 25(OH)D from those with only a small increase from just below to above 37 nmol/l. However, in a sensitivity analysis, we did not identify a trend suggesting that an increase in 25(OH)D of >20 nmol/l, from <25 nmol/l in early pregnancy, was associated with any of the neonatal anthropometric measures, when compared with neonates of women with consistently sufficient levels. In addition, eligible neonates without study-specific measurements were missed at random because of logistic reasons, for example, holidays and temps not familiar with the study and hence not reporting the birth to the study midwives[5].

Interpretation

First, before including ethnicity in the analyses, we found a strong association between maternal 25(OH)D and birth weight. This is in line with several other observational studies, although results are inconsistent. Four systematic reviews (meta-analyses) have found a positive association between maternal 25(OH)D status or vitamin D supplementation and birth weight[14–17]. In line with our study, seven cohort studies found no association between maternal 25(OH)D and birth weight[31–35], whereas three found a positive association[20–22]. A recent Cochrane review[19] and previous meta-analysis of RCT[14–18,36–40], show inconclusive results regarding the effect of birth weight.

Furthermore, we found that the association between maternal 25(OH)D and birth weight disappeared after adjusting for ethnicity. The effect of ethnicity as a confounder may, however, represent other aspects than ethnicity *per se*. Skin colour affects the production of 25(OH)D in the skin as a response to sunlight, but could also be considered a proxy measure of

Table 4. Associations between 25-hydroxyvitamin D (25(OH)D) (continuous and categorically) in pregnancy and small for gestational age (SGA) (*n* 758)* (Odds ratios and 95 % confidence intervals)

		Univariate analysis			Multiple analysis (model 1)†			Multiple analysis (model 2)‡§		
Outcomes	*n*	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
SGA										
25(OH)D at GW 15	744	0·99	0·98, 1·0	0·01	0·99	0·98, 1·0	0·01	1·0	0·99, 1·0	0·62
SGA										
Consistently sufficient (Ref)‖	398									
Decreasing¶	62	1·4	0·67, 2·9	0·37	1·5	0·68, 3·2	0·33	1·2	0·52, 2·6	0·72
Increasing**	139	1·5	0·89, 2·6	0·12	1·7	0·94, 2·9	0·08	1·1	0·57, 2·0	0·86
Consistently deficient††	108	2·0	1·1, 3·4	0·02	2·1	1·2, 4·0	0·02	1·3	0·66, 2·5	0·47

GW, gestational week; Ref, referent values; AIC, Akaike's information criterion.
* Generalised logistic regression analysis with SGA (birth weight <10th percentile according to Norwegian national references) as a dependent variable. Preterm included (*n* 39)
† Adjusted model 1; multiple regression, additional adjustment for neonate sex, gestational age, season, maternal age, parity, educational level and prepregnancy BMI.
‡ Adjusted model 2; as model 1, with additional adjustment for geographic origin.
§ Pregnancy: *n* 729, AIC = 562; SGA: *n* 693, AIC = 535.
‖ Consistently sufficient: 25(OH)D ≥ 37 nmol/l at GW 15 and 28.
¶ Decreasing: 25(OH)D ≥ 37 nmol/l at GW 15 and <37 at GW 28.
** Increasing: 25(OH)D < 37 nmol/l at GW 15 and ≥37 at GW 28.
†† Consistently deficient: 25(OH)D < 37 nmol/l at GW 15 and 28.

socioeconomic status[41,42]. Some other studies indicate that lower birth weight in ethnic minority groups seems to be linked to maternal early life factors among others, and may be transmitted over generations[8,10,43]. In general, few studies have explored these relationships in a multiethnic population, and few have included the same ethnicities as in our study[22,23]. In one of these studies, an association was found with 25(OH)D <30 nmol/l[21]. Another study adjusted for few confounders, and ethnicity was poorly defined, making comparison for specific ethnic groups difficult[22]. Recently, a large study from the Netherlands found a positive association between maternal 25(OH)D measured once in pregnancy, and fetal growth, birth weight, length and head circumference at birth[20], indicating a difference in birth weight of approximately 80 g between those with low levels compared with optimal levels of 25(OH)D. However, only estimates for differences in *z* score – adjusted for a large number of maternal factors – were reported, making comparison difficult. We can only speculate on the reasons for the discrepancy between our study and the two studies from the Netherlands[20,21]. We cannot rule out that the biological effect of 25(OH)D could differ between the populations. One potential factor could be genotypes coding for the vitamin D receptor, vitamin D binding protein and regulatory enzymes; which may all differ by ethnicity and be potential effect modifiers[44,45]. In addition, the ethnic and socioeconomic composition of our sample differed somewhat from the two Dutch studies. The relation between these sociodemographic factors and 25(OH)D, and also birth weight, may differ between populations. Hence, it is more likely that this difference in results between studies is a result of residual confounding.

As in many other studies, we examined the association between 25(OH)D and birth size as a continuous outcome. However, others have argued that this may be problematic, as 25(OH)D may be more strongly related to pathological fetal growth, such as SGA, than in accounting for variation in normal fetal growth[44]. Furthermore, the relationship may not be linear, but U-shaped, although this was not found in our study. Moreover, optimal fetal growth may differ between ethnic groups, and actually remains to be defined. The mean birth weight of Asian neonates is several hundred grams lower than that of European neonates[8,46]. Hence, applying a universal standard for SGA would lead to more Asians being diagnosed as SGA than Europeans, with the Asian group probably including a higher proportion of constitutionally small babies.

When it comes to associations between 25(OH)D and other anthropometric measures, studies are fewer[14]. We found a strong association between maternal 25(OH)D and head circumference, abdominal circumference and sum of skinfolds. Also for these outcomes the association disappeared after adjusting for ethnicity. In a recent Cochrane review[19] there was some indication that maternal treatment during pregnancy may increase infant length and head circumference at birth. In some observational studies no associations were found between 25(OH)D and birth length and head circumference after adjusting for confounders[23,31–35,47], whereas other studies found an association[14,20]. We identified only four observational cohort studies of the association between 25(OH)D and skinfold thickness and circumferences[14,23]. Two studies found an association[31,33] whereas two did not, in line with our study[23,32]. A study measuring body composition by dual energy X-ray absorptiometry found a positive association between 25(OH)D and offspring fat mass at birth[48]. Recently, a multiethnic study of an Asian population (Chinese, Malay or Indian) from Singapore reported several anthropometric measures and found no associations between maternal 25(OH)D and any of the birth outcomes, including skinfolds and abdominal circumference, in line with our study[23]. This study adjusted for ethnicity and approximately the same explanatory factors as we did. This study sample had a low prevalence (1·6 %) of severe maternal deficiency. Hence, our study with high prevalence of severe deficiency may complement their findings.

However, we observed an interaction with sex, indicating that increased maternal 25(OH)D during pregnancy was associated with less subcutaneous fat in boys only. Interestingly, we also found an interaction between 25(OH)D and sex for the outcome abdominal circumference, indicating that there may be a differential effect of 25(OH)D depending on whether the fetus is a boy

or a girl. To our knowledge, this has not been reported from previous studies, but is in accordance with studies suggesting sex-specific responses to an adverse fetal environment[29]. Nevertheless, the clinical implications of these results are unknown.

Implications for practice/research

From a public health perspective and according to the Cochrane review there is still a need for high-quality RCT studies in vitamin D-deficient pregnant populations on the effect of vitamin D supplementation on clinically important neonatal outcomes other than bone health. In a European context, a vitamin D-deficient population will mostly consist of women of non-Western origin. Further, there is a need to study subtle differences in phenotypes and possible sex differences in the effect for some outcomes.

Conclusion

To conclude, our study did not identify any associations between levels of vitamin D during pregnancy and a wide range of anthropometric measures of the newborn. The possibility of a sex-specific response to low levels of vitamin D during pregnancy warrants further studies. However, our study cannot rule out possible detrimental effects on the newborn not reflected in anthropometric data.

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A. K. J. initiated the STORK Groruddalen study. L. S. participated in data collection. Å. R. E., K. V. K. and A. K. J. designed the sub-study. Å. R. E. prepared the first version of the manuscript. A. K. J., I. M., K. V. K., L. S. and P. L. contributed to the discussion and results. Å. R. E. and I. M. performed the statistical analyses. All authors have revised the manuscript and approved the final version.

The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711451700068X

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